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lymphedema. Other surgical interventions, including lymph node transfer, are rarely used and often not successful in ameliorat ing lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system and may improve lymphatic transport and quality of life in secondary lymphedema. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility. Modification of surgi cal techniques to minimize impact upon the lymphatic system or enhance drainage with prophylactic lymphatic-venous shunts are being employed during operations that require lymph node dis section to reduce the risk of lymphedema. Therapeutic lymphangiogenesis has intriguing potential as it has been studied in animal models of lymphedema. Overexpres sion of VEGF-C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema. The administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of postsurgical lymph edema. There may be additional benefits when administered in conjunction with lymph node transfer. However, clinical trials in patients with lymphedema are still required to determine efficacy of gene transfer and cell-based therapies for lymphedema. ■ ■FURTHER READING Aspelund A et al: Lymphatic system in cardiovascular medicine. Circ Res 118:515, 2016. Brouillard P et al: Genetics of lymphatic anomalies. J Clin Invest 124:898, 2014. Executive Committee: The diagnosis and treatment of peripheral lymphedema: 2020 consensus document of the International Society of Lymphology. Lymphology 53:3, 2020. Gloviczki P et al: The 2022 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clini cal practice guidelines for the management of varicose veins of the lower extremities. Part I. Duplex Scanning and Treatment of Super ficial Truncal Reflux. J Vasc Surg Venous Lymphat Disord 11:231. e6, 2023. Jayaraj A, Gloviczki P: Chronic venous insufficiency, in Vascular Medicine, MA Creager, JA Beckman, J Loscalzo (eds). Philadelphia, Elsevier, 2020, pp 709-727. Kahn SR et al: The postthrombotic syndrome: Evidence-based preven tion, diagnosis, and treatment strategies: A scientific statement from the American Heart Association. Circulation 130:1636, 2014. Lurie F et al: The American Venous Forum, American Vein and Lym phatic Society and the Society for Vascular Medicine expert opinion consensus on lymphedema diagnosis and treatment. Phlebology 37:252, 2022. Masuda E et al: The 2020 appropriate use criteria for chronic lower extremity venous disease of the American Venous Forum, the Society for Vascular Surgery, the American Vein and Lymphatic Society, and the Society of Interventional Radiology. J Vasc Surg Venous Lymphat Disord 8:505.e4, 2020. Rabinovich A, Kahn SR: The postthrombotic syndrome:

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Bradley A. Maron, Joseph Loscalzo

Pulmonary Hypertension CHAPTER 294 Pulmonary hypertension (PH) is a heterogeneous disease involving pathogenic remodeling of the pulmonary vasculature, which increases pulmonary artery pressure and pulmonary vascular resistance (PVR). The most common causes of PH are left heart or primary lung disease. Additionally, PH is observed in some patients as a later complication of luminal pulmonary embolism and may be observed variably in patients with various hematologic, myeloproliferative, and other systemic dis eases. Pulmonary arterial hypertension (PAH) is an uncommon, but distinct, PH subtype characterized by the interplay between molecular and genetic events that cause an obliterative arteriopathy and symp toms of dyspnea, chest pain, and syncope. If left untreated, PH carries a high mortality rate, largely owing to decompensated right heart failure. Pulmonary Hypertension There have been significant advances in diagnosis, classification, and treatment of PH patients. For example, the mean pulmonary artery pressure (mPAP) used to diagnose PH has been lowered from ≥25 mmHg to >20 mmHg, and the PVR level used to identify patients with PAH and other forms of precapillary PH has been lowered from ≥3 to

> 2 Wood units (WU). These adjustments emphasize earlier disease detection, as a substantial delay in diagnosis of up to 2 years is common in PAH and has important implications for both quality of life and life span. Clinicians should be able to recognize the signs and symptoms of PH and complete a systematic evaluation in at-risk patients. In this way, prompt diagnosis, appropriate treatment, and optimized patient outcome are achievable. ■ ■PATHOBIOLOGY Apoptosis resistance, cell proliferation, dysregulated metabolism, and increased oxidant stress involving pulmonary vascular cells, pericytes, and adventitial fibroblasts underlie the pathogenesis of PAH. These events lead to hypertrophic, fibrotic, and plexogenic remodeling of distal (small) pulmonary arterioles, which decreases vascular compli ance and promotes in situ thrombosis (Fig. 294-1). The remodeling pattern also includes extracellular matrix expansion, which is rich in integrins, nonfibrillar collagens, fibronectin, and other tensile proteins that stiffen affected blood vessels further. A minority of patients appear to have a vasoconstriction-dominant phenotype, which, if present, requires a unique treatment strategy discussed in greater detail below. There is now greater understanding that in PAH, right ventricular dys function occurs due not only to increased right ventricular afterload but also as a consequence of depressed right ventricular sarcomere function from chronic inflammation or autoimmune mechanisms. Genetic Drivers Several germline variants in genes that regulate

> fundamental cellular processes such as growth, proliferation, or pheno type switching are associated with incident PAH and follow a familial pattern. A variant in the gene encoding bone morphogenetic protein receptor-2 (BMPR2) is the most common cause of hereditary PAH, although penetrance is variable and may be as low as 20% in some populations. Sporadic mutations involving BMPR2 are also reported in PAH patients. BMPR2 is within the (super)family of transforming growth factor- β (TGF-β) receptors that transduce a wide range of cellular events via stimulation by activins, inhibins, and bone morpho genetic proteins (Fig. 294-2). Indeed, imbalance between proliferative and antiproliferative TGF-β receptor signaling in PAH has emerged as a bona fide therapeutic target based on clinical trials testing the effect of activin signal inhibitor therapy on outcome in PAH (see section on sotatercept). The advance of genome-wide association studies has expanded the range of genetic drivers linked to pathogenic mechanisms underly ing PAH, to include TBX4 and SOX17, which regulate activation of fibroblast growth factor-10 and hepatocyte growth factor, respectively. Genetic predisposition to PH in the setting of left heart disease is unresolved, although single-gene polymorphisms that target actin

PART 6 Disorders of the Cardiovascular System Br A B C D E F FIGURE 294-1 Panels on the left show examples of plexogenic pulmonary arteriopathy. Representative images of a normal lung (A) and examples of pulmonary vascular remodeling in pulmonary arterial hypertension (B–F), including idiopathic pulmonary arterial hypertension (B–E) and pulmonary venoocclusive disease (F), are shown. A. Normal pulmonary artery (arrow) adjacent to a terminal bronchiole (Br). B. Marked media and intima thickening of small vessels (arrow), partly surrounded by lymphoid cells, form a cluster reminiscent of a primary follicle (arrowhead). C. Idiopathic pulmonary hypertension lung with a markedly muscularized medium-sized pulmonary artery (arrow), which distally branches into a plexiform lesion (lower arrowhead) and an adjacent plexiform lesion (upper arrowhead). D. Complex vascular lesion (circle) with a combination of telangiectatic-like dilations of the pulmonary artery (arrowheads) and a plexiform lesion (arrow). E. Medium-sized pulmonary artery with complete lumen obliteration with a loose collagen, poorly cellular matrix (arrows). F. Interlobular septal, medium-sized vein (arrowhead) obliterated by loose connective tissue (arrows), likely the result of an organized thrombus, characteristic of venoocclusive disease. (These representative images were provided courtesy of Dr. Rubin Tuder. The samples were obtained through the evaluation of lungs collected by the Pulmonary Hypertension Breakthrough Initiative, with similar pulmonary vascular pathology spectrum as reported in reference E Stacher et al: Modern age pathology of pulmonary arterial hypertension. Am J Respir Crit Care Med 186:261, 2012. Adapted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved. Reproduced with permission from BA Maron et al: Pulmonary Arterial Hypertension: Diagnosis, Treatment, and Novel Advances. Am J Respir Crit Care Med 203:1472, 2021.) binding, basement membrane, and major histocompatibility complex II proteins have been reported in lung tissue of affected patients. A variant in EIF2AK4 is an established genetic risk factor for pulmonary venoocclusive disease with a recessive mode of transmission, although clinical expression among carriers is evident initially across a wide age range (10–60 years). Epigenetics in PH The baseline DNA damage profile is increased in pulmonary artery

endothelial cells and circulating blood mononuclear Pulmonary arterial hypertension Antiproliferative BMPs BMPR-II ALK 1/2/3/6 pSmad1/5/8 Smad4 pSmad2/3 Extracellular Gremlin-1 and noggin FIGURE 294-2 Pulmonary arterial hypertension is associated with dysregulation of the bone morphogenetic protein (BMP) receptor type II (BMPR-II)–Smad1/5/8 pathway in pulmonary vascular smooth muscle and endothelial cells, causing an imbalance between proproliferative and antiproliferative signaling pathways. BMPR-II–Smad1/5/8 pathway downregulation leads to increased production of activin ligands, such as activin A, growth differentiation factor 8 (GDF8), and GDF11, which contributes to activin receptor type IIA (ActRIIA)–Smad2/3 pathway upregulation. Increased phosphorylated Smad (pSmad) 2/3 activity promotes expression of the endogenous BMP antagonists gremlin-1 and noggin. Gremlin-1 and noggin further reduce BMP–Smad1/5/8 signaling. The overall result is that antiproliferative signaling is reduced, shifting the balance toward proproliferative activin–Smad2/3 signaling, which leads to pulmonary vascular remodeling. (Adapted from M Humbert et al: N Engl J Med 384:1204, 2021.)

cells from PAH patients. This finding implicates DNA itself as a target of injury and is accompanied by epigenetic disease mechanisms involv ing methylation and demethylation that include translocation methyl cytosine dioxygenase 2 (TET2) and methyltransferase 3B (DNMT3B). The extent to which these events are transmissible across generations remains limited to experimental disease models. Nevertheless, bromo domain-containing 4 and histone deacetylation inhibition, particularly for HDAC-1 and HDAC-5, are promising future PAH therapeutics. Long noncoding RNAs, which regulate epigenetic (among other) Activins and GDFs Proproliferative ALK 4/5/7 ActRIIA/B

processes that underpin hypertrophic vascular remodeling in PAH, include the tyrosine kinase receptor–inducing long noncoding RNA through its effects on p53/platelet-derived growth factor receptor β in lung pericytes. At present, hypoxia is the most well-studied epigenetic driver linked to PH, but a practical framework to predict disease onset through this mechanism in individual patients is unresolved. Endothelial-Mesenchymal Transition Plexigenic and fibrotic pulmonary arterial remodeling in PAH is linked to cellular phenotype switching, particularly endothelial-mesenchymal transition (End-MT) for which specific markers are identified in ~6% of cells in explanted lungs from patients or at autopsy. Inflammation as well as hypoxia plus vascular endothelial growth factor receptor inhibition have been shown to increase End-MT, which in affected cells is characterized by migration, gain of smooth muscle actin fibers, and loss of cell-cell con tacts. Interestingly, End-MT is related to a loss of BMPR2 expression, tying together a monogenic risk to a key endophenotype that drives PAH pathology. Hypoxia, Metabolism, and Matrix Remodeling Abnormali ties in multiple molecular pathways, genes, and cell types are associated with potentially modifying therapeutics, particularly those that focus on extracellular matrix remodeling (Fig. 294-3). The tyrosine kinase Janus kinase 2 (JAK2) is overactivated in PAH, which is inhibited by ruxolitinib to attenuate cellular proliferation and experimental PH. Hypoxia-inducible factor (HIF) signaling is a potentially modifiable disease-causing pathway, as treatment with the novel HIF-2α inhibitor PT2567 improves hemodynamics and vascular remodeling in PAH. Classical treatment Sotatercept

BMPR2mediated ET-1 Activin L-Arginine NOS AA ActRIIA/B ET-1 L-citrulline GFs/ cytokines pSmad2/3 pSmad1/5/8 Prostacyclin derivatives NO PGI2 ETA/ETB2 sGC stimulator

Epigenetic/TF: -DNMT3B -HIF-1/HIF-2 -SOX9 -SOX17 -TBX4 -TET2 -TWIST-1 -TYKRIL ETA/ETB2 antagonists PDE5 inhibitor Vasoconstriction äProliferation Vasodilation åProliferation Fibroblast Immune cell PAEC PASMC Pericyte FIGURE 294-3 Modifiable pathobiological targets in pulmonary arterial hypertension. Current treatment approaches focus on endothelin, nitric oxide, and prostacyclin signaling. Novel treatment targets address (1) epigenetic mechanisms/transcriptional factors; (2) oxidative stress; (3) hypoxia and metabolic signaling; (4) BMPR2mediated signaling; (5) tyrosine kinase and growth factor signaling; (6) fibrosis and extracellular matrix remodeling; and (7) inflammation and immune cell infiltration. 4PBA, 4-phenylbutyric acid; AA, arachidonic acid; ActRII, activin receptor type II; BMP, bone morphogenetic protein; BMPR2, bone morphogenetic protein receptor type 2; cDC, conventional dendritic cell; DNMT3B, DNA methyltransferase 3 b; ET, endothelin; GDFs, growth and differentiation factors; HIF = hypoxia-inducible factor; JAGGED-1, jagged canonical Notch ligand 1; JAK, Janus kinase; MAO-A, monoaminoxidase A; MMP, matrix metalloproteinase; NUDT1, nudix hydrolase 1; NEDD9, neural precursor cell–expressed developmentally downregulated protein 9; NFU1, NFU1 iron-sulfur cluster scaffold; NO, nitric oxide; NOS, nitric oxide synthase; PAEC, pulmonary artery endothelial cell; PASMC, pulmonary arterial smooth muscle cell; PDE5, phosphodiesterase 5; PGI2, prostacyclin; PINK1, phosphatase and tensin homolog–induced kinase 1; SDF1, stromal cell–derived factor 1; sGC, soluble guanylate cyclase; SOX9, SRY-box transcription factor 9; SOX17, SRY-box transcription factor 17; SPARC, secreted protein acidic and rich in cysteine; TBX4, T-box transcription factor 4; TET2, Tet methylcytosine dioxygenase 2; TWIST1, Twist family BHLH transcription factor 1; TYKRIL, tyrosine kinase receptor–inducing long noncoding RNA. (Reproduced with permission from SJ Johnson et al: Am J Respir Crit Care Med 208:528, 2023.)

Pulmonary artery smooth muscle cells isolated from PAH patients preferentially synthesize lactic acid in the presence of abundant molecular oxygen (Warburg effect). This metabolic change results in a proliferative cellular phenotype and has stimulated intense interest on metabolic modulating therapies. Dichloroacetate, which inhibits pyruvate dehydrogenase kinase to normalize voltage-gated K+ chan nels and promote pulmonary artery smooth muscle cell apoptosis, has been tested clinically with overall mixed results but a signal toward predicting treatment response by SIRT3 and UCP2 genotype. Nonetheless, numerous alternative metabolic targets show therapeutic promise, including SOD2, PPARγ, and NFAT. Finally, there is greater interest in reverse remodeling pathways in PAH. For example, matrix metalloproteinase (MMP)-8 is protective against PAH by stabiliz ing mechanosensitive focal adhesion kinase–yes-associated protein/ transcriptional coactivator with PDZ-binding motif (FAK-YAP/TAZ). This stabilization, in turn, suppresses extracellular matrix expansion and vascular fibrosis.

CHAPTER 294 Pulmonary Hypertension ■ ■PATHOPHYSIOLOGY In PAH, plexogenic and fibrotic remodeling of pulmonary arterioles impairs pulmonary arterial compliance and results in a progressive increase in total PVR. The resting PVR increases through the temporal progression of PAH, corresponding to a rise in mPAP. To preserve cardiac output (CO) in the face of elevated right ventricular afterload, right ventricular work must increase. A sustained (or progressive) increase in right ventricular work causes a shift in the efficiency of right ventricular systolic function by which maintaining pulmonary New treatment

Inflammation/ Immune cells: -cDCs -T-cells -JAGGED-1 4PBA BMP9/10

Tyrosine kinase/ Growth factors Degradation

Fibrosis and ECM remodeling: -MMP-8 -NEDD9 -SPARC BMPRII -Capmatinib -Crizotinib -Imatinib -Seralutinib JAK2 Ruxolitinib

Hypoxia/metabolism: -Glutaminolysis -Glucose/Prolin -HIF-2` -NFU1 -PINK1 -Sirtuin 3 Clorgyline Oxidative stress -MAO-A Oxidative stress PT2567 NDUT1 (S)-Crizotinib SDF1

RISK STRATIFICATION EARLY AND AGGRESSIVE INTERVENTION Dual Pharmacotherapy Prescription Exercise Treat Systemic Targets Intervention Focus PART 6 Disorders of the Cardiovascular System Genetic Screen Exercise Testing Developmental Screen Clinical “Stage” A CO Hemodynamic PAP PVR RAP Histologic SMC Elastin Pericyte EC Structural Adv. Fibroblast Proliferation of fibroblasts and SMCs, swelling of ECs, and fragmented elastin Endothelial channel formation Smooth muscle–like cells encroach on lumen inflammation Time FIGURE 294-4 An integrated overview of pulmonary arterial hypertension (PAH). In PAH, initial changes in the histopathophenotype of distal pulmonary arterioles precede significant changes in hemodynamics or the development of symptoms in most patients (clinical stage A). As vascular remodeling progresses, there is an increase in pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), and right atrial pressure (RAP). In clinical stage B, symptoms are evident and, when diagnosed, prompt early, aggressive treatment. Effacement of pulmonary arterioles results in severely increased PVR that promotes right heart failure, defined by a decrease in cardiac output (CO) and PAP. Patients in clinical stage C have severe symptoms and require full therapeutic intervention. Identifying clinical stage A patients remains challenging, although genetic risk factors or symptoms with exercise may be informative. EC, endothelial cell; SMC, smooth muscle cell. (Reproduced with permission from Maron BA, Abman SH: Focusing on Developmental Origins and Disease Inception for the Prevention of Pulmonary Hypertension. Am J Respir Crit Care Med 195:292, 2017.) circulatory pressure depletes myocardial energy. These changes occur at the expense of energy normally reserved to maintain optimal blood perfusion through the alveolar-capillary interface for blood oxygenation, a process termed right ventricular–pulmonary arterial uncoupling. In end-stage PAH, the CO declines, leading to a decrease in mPAP (Fig. 294-4), with extrapulmonary vascular manifestations. These include overactivation of neurohumoral signaling, renal failure, abnormal episcleral vessels (seen in patients with hereditary PAH due to BMPR2 mutation), and hyper- or hypothyroidism. Volitional muscle atrophy in PAH is associated with reduced muscle strength, type I fiber switching to fatigable type II fibers, and decreased capillary density. This myopathy affects respiratory function, as well, including impair ment of maximal inspiratory and expiratory pressure. Overall, sarcope nia in PAH with right ventricular heart failure is likely multifactorial, driven by deconditioning and alternative pathophysiological mecha nisms linked to impaired cardiac output (i.e., neurohumoral signaling) and possibly through the ectopic effects of molecular intermediaries such as miR-136 downregulation (Fig. 294-5). ■ ■DIAGNOSIS The diagnosis of PH can be missed without a reasonable index of sus picion. Indeed, findings from clinical registries suggest that PH is often overlooked, even among patients with numerous risk factors. This shortcoming may be because PH symptoms are nonspecific, insidi ous, and overlap considerably with many common conditions, such as asthma, heart failure with preserved ejection fraction, and decon ditioning. Additionally, there is a misconception that in patients with comorbid cardiopulmonary conditions (e.g., interstitial lung disease, mitral valve disease), PH is merely an extension of the underlying dis ease rather than a specific clinical entity.

FULL INTERVENTION Maximal Medical Therapy Surgical Referral B C Inflamatory Cell Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and syncope are less common and associated with more advanced disease. In early phases of PAH, the physical examination is often unrevealing. As the disease progresses, there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P2 component of the second heart sound, a right-sided S3 or S4, and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are commonly concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma (or the limited cutaneous form, CREST [calci nosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia]), and crackles on examination of the lungs and systemic hypertension may be clues to left-sided systolic or diastolic heart failure. Overview of the Diagnostic Clinical Evaluation Once clini cal suspicion is raised, a systematic approach to diagnosis and assessment is essential. In advanced disease, electrocardiography may show right ventricular hypertrophy or strain, and enlargement of pulmonary arteries and obliteration of the retrosternal space are often observed on chest roentgenography (Fig. 294-6). In turn, echocardiography with agitated saline (bubble) study is the most important initial screening test. Elevated estimated pulmonary artery systolic pressure (>35 mmHg), notched waveform on continuous wave Doppler interrogation of the right ventricular outflow tract, or a hypertrophied or dilated right ventricle supports the diagnosis of PH. Important additional information can be gleaned about specific etiologies of PH, such as valvular disease, left ventricular systolic

Eyes: • Open-angle glaucoma • Retinal detachment • Venous stasis retinopathy • Central retinal vein occlusion Thyroid: • Hypothyroidism • Hyperthyroidism • Grave's disease Liver: • Congestive hepatopathy • Hepatic fibrosis • Cardiac cirrhosis • Ischemic hepatitis Iron homeostasis: • Iron deficiency • Impaired absorption • Anemia Endocrine system: • Metabolic syndrome • Diabetes • Estrogen/testosterone Immune system: • Systemic inflammation • Innate/adaptive immunity • Autoimmunity Skin: • Subacute prurigo simplex FIGURE 294-5 Systemic manifestations of right heart failure. (Reproduced with permission from S Rosenkranz et al: Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation 141:67, 2020.) dysfunction, left atrial enlargement, and intracardiac shunt. In addi tion, hypertrophic cardiomyopathy (HCM), amyloid cardiomyopathy, and sarcoid cardiomyopathy, which are specific forms of left heart dis ease that predispose to PH, are linked to disease-specific approaches to treatment. A high-quality echocardiogram that is absolutely normal may obvi ate the need for further PH evaluation. However, this is distinct from an echocardiogram in which tricuspid regurgitation is not detected. In this scenario, the information required to estimate pulmonary artery pressure is lacking, and PH is observed in one-third of such patients. Patients with evidence of PH on echocardiography or in whom unex plained dyspnea or hypoxemia is evident despite an unremarkable echocardiogram often require further assessment. Additional tests focusing on functional capacity are useful for quan tifying disease burden, such as a 6-minute walk distance (6-MWD) assessment, which also aids in assessing prognosis. Cardiopulmonary exercise testing (CPET) may differentiate between cardiac and pul monary limitations to exercise thereby providing pathophysiologic insights on the cause of dyspnea. Peak volume of oxygen consumption (pVO2), which is an integrated parameter of cardiopulmonary fitness, is prognostic in PH patients when <15 mL/kg/min. However, low pVO2 is an important clinical finding across the spectrum of heart-lung disease and, thus, is not diagnostic of PH per se. In patients with a normal CPET, further invasive testing is often

unnecessary. One exception to this approach is in patients with reassuring CPET results but in whom a significant decrease in exercise tolerance from baseline is nonetheless reported, often observed in elite athletes or highly conditioned indi viduals with early-stage PH or subacute pulmonary embolism.

Brain: • Cognitive function • Depression • Anxiety • Sleep CHAPTER 294 Autonomic system: • Sympathetic hyperactivity • Increased susceptibility for syncope and arrhythmias • Endothelial dysfuntion Pulmonary Hypertension Left heart: • Mechanical compression • Underfilling/deconditioning • Functional (systolic/diastolic) • Cardiomyocyte atrophy Kidneys: • Low perfusion renal injury • Congestive nephropathy • Renal fibrosis/sclerosis • “Acute-on-chronic” renal injury Gut/Bowel: • “Leaky bowel syndrome” • Malabsorption • Appetite loss/cachexia • Gut microbiota Skeletal muscle: • Deconditioning • Impaired function of skeletal and respiratory muscles • Reduced aerobic capacity Invasive hemodynamic monitoring with right heart catheterization (RHC) is the gold standard for PH diagnosis and severity assessment. Interpretation of RHC data, however, is often optimized by informa tion from diagnostic tests that support and frame the clinical context of pulmonary vascular disease. Stepwise Approach to Diagnosing PH One common PH diagnostic strategy is outlined in Figure 294-7; however, the approach should be individualized in practice according to a particular patient’s clinical and risk factor profile. For example, patients with a strong his tory of inhaled tobacco use may benefit from prioritizing diagnostic tests assessing pulmonary function and the lung parenchyma, whereas a myocardial ischemia evaluation should be considered early in the evaluation of patients with left-sided cardiomyopathy. PULMONARY FUNCTION AND LUNG IMAGING Pulmonary function testing results may suggest restrictive or obstructive lung diseases as the cause of dyspnea or PH. In PAH, an isolated reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) is a classic finding. High-resolution computed tomography (CT) provides useful informa tion, particularly enlargement of the main pulmonary artery, right ventricle, and atria, as well as peripheral pruning of small vessels; how ever, high-resolution CT may also reveal signs of venous congestion, including centrilobular ground glass infiltrate and thickened septa. In the absence of left heart disease, these findings suggest pulmonary venous disease, a rare cause of PAH that can be quite challenging to diagnose. CT is also critical for distinguishing comorbid interstitial lung disease, emphysema, or overlap syndromes that include fibrosis and obstructive pulmonary disease.

PART 6 Disorders of the Cardiovascular System A B C E FIGURE 294-6 Electrocardiography, chest roentgenography, and two-dimensional echocardiography in advanced pulmonary arterial hypertension. A. Standard 12-lead electrocardiogram shows peaked R waves in lead V1 and ST-segment depression in leads V2–V3, suggestive of right ventricular hypertrophy with strain (arrows). B, C. Anterior-posterior and lateral chest roentgenogram demonstrating enlargement of central pulmonary arteries and obliteration of the retrosternal space, indicative of right ventricular hypertrophy. D, E. Apical four-chamber and two-chamber short axis views acquired by transthoracic echocardiography demonstrate right ventricular (RV) and right atrial (RA) enlargement, as well as interventricular septal flattening in diastole consistent with pressure overload. LV, left ventricle. SLEEP STUDIES Nocturnal desaturation is a common finding in PH, even in the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnea or obesity-hypoventilation syndrome are present. ASSESSMENT OF PULMONARY ARTERIAL THROMBOSIS Patients with prior luminal pulmonary embolism are at increased risk for chronic Right Heart

Catheterization mPAP >20 mmHg Identify Hemodynamic Classification Pre-Capillary PH PVR >2.0 WU; PAWP ≤15 mmHg Isolated Post-Capillary PH PVR ≤2.0 WU; PAWP >15 mmHg Combined Pre-/Post-Capillary PH PVR >2.0 WU; PAWP >15 mmHg Clinical Group Clinical Group 1: PAH, PVOD, CHD, others 2: Chronic lung disease and hypoxia 4: CTEPH 5: Multi-factorial PH 3: LHD FIGURE 294-7 Integrating the cardiopulmonary hemodynamic and clinical profile of patients with pulmonary hypertension (PH). Diagnosing PH is achieved by right heart catheterization and requires a mean pulmonary artery pressure (mPAP) >20 mmHg. Patients are then classified by hemodynamic category, which together with the clinical profile and other supporting data (e.g., chest imaging, serology, genetic testing) is used to determine the PH clinical group. Certain clinical groups are incompatible with hemodynamic classifications; for example, pulmonary arterial hypertension (PAH) cannot be diagnosed in patients with isolated postcapillary or combined pre-/ postcapillary PH hemodynamics. CHD, congenital heart disease; CTEPH, chronic thromboembolic PH; LHD, left heart disease; PAWP, pulmonary artery wedge pressure; PVOD, pulmonary venoocclusive disease; PVR, pulmonary vascular resistance. (Reproduced with permission from BA Maron et al: Cardiopulmonary hemodynamics in pulmonary hypertension and heart failure: JACC Review Topic of the Week. J Am Coll Cardiol 76:2671, 2020.)

RV RA D RV LV thromboembolic pulmonary hypertension (CTEPH), which is a spe cific PH subtype characterized by vascular fibrosis and arterial micro thrombus. Although CTEPH is curable in many patients by surgical endarterectomy, it is also widely underdiagnosed. Ventilation-perfusion (V./Q.) scanning is still the primary test used to screen and diagnose CTEPH, which should be considered in any patient with PH of unclear etiology. Nonetheless, CT angiography is increasingly used in clinical Clinical Group 3: Chronic LHD 4: CTEPH (rare) 5: Multi-factorial PH

practice to manage CTEPH especially for staging anatomic throm boembolic burden, which may be ultimately necessary to determine operative candidacy. The definitive diagnostic procedure is digital subtraction pulmonary angiography since contrast enhancement in this study provides detailed information on webbing, stricture, and vascular tapering patterns pathognomonic for CTEPH. SEROLOGY Laboratory data that are important for screening include a human immunodeficiency virus (HIV) test when clinically indicated. In addition, all patients should have antinuclear antibodies, rheuma toid factor, and anti-Scl-70 antibodies assessed to screen for the most common rheumatologic diseases associated with PH. Liver function and hepatitis serology tests are important to screen for underlying liver disease. Methamphetamine use is recognized increasingly as a cause of PAH, and screening should be considered in patients from endemic regions or in whom the cause of PAH is not otherwise established. Finally, brain natriuretic peptide (BNP) and the N-terminus of its propeptide (NT-proBNP) correlate with right ventricular dysfunction, hemodynamic severity, and functional status in PAH. Medical therapy also lowers NT-proBNP levels in PAH, and therefore, this test may be used as a biomarker for assessing treatment response in clinical prac tice once a baseline level is established. INVASIVE CARDIOPULMONARY HEMODYNAMICS The RHC remains the gold standard test to both establish the diagnosis of PH and guide selection of appropriate medical therapy. The hemodynamic criteria for diagnosing PH requires, first, an mPAP >20 mmHg. Precapillary and postcapillary PH are then distinguished by virtue of a pulmo nary artery wedge pressure (PAWP) (or left ventricular end-diastolic pressure [LVEDP]) ≤15 mmHg or >15 mmHg, respectively. Isolated precapillary PH also requires a PVR >2.0 WU, whereas isolated post capillary PH is defined by PVR ≤2.0 WU. Increasingly, combined pre- and postcapillary PH is recognized, defined by elevated mPAP

20 mmHg, PVR >2.0 WU, and PAWP >15 mmHg (Fig. 294-7). These hemodynamic profiles inform PH clinical categorization. For example, isolated precapillary PH is most often due to primary lung disease, PAH, or CTEPH. Isolated postcapillary PH occurs in patients with mitral valvular disease, left ventricular systolic dysfunction, heart failure with preserved ejection faction, HCM, and amyloid cardiomy opathy. The same etiologies for isolated postcapillary PH also underlie combined pre- and postcapillary PH. When present, this indicates that chronic vascular congestion due to left atrial hypertension has resulted in substantial pulmonary vascular remodeling, although the precise mechanisms that transition patients from isolated postcapillary PH to combined pre-/postcapillary PH are not known. Patients with left heart disease risk factors who are diuresed aggressively prior to RHC may appear to have an isolated precapillary PH profile, tempting a diagnosis of PAH. However, these patients require specific consideration given the potential effects of diuresis on masking the true underlying PH hemodynamic classification. Vasoreactivity testing should be reserved for patients with idiopathic or hereditary PAH. Vasodilators with a short duration of action, such as inhaled nitric oxide (NO•) or inhaled epoprostenol, are preferred for testing. A decrease in mPAP by ≥10 mmHg to an absolute level ≤40 mmHg without a decrease in CO is defined as a positive pulmo nary vasodilator response, and such responders are considered for long-term treatment with calcium channel blockers. Less than 5% of patients are deemed vasoreactive, although prognosis among these patients is particularly favorable. ■ ■PULMONARY HYPERTENSION CLASSIFICATION The current classification system, last revised in 2018 during the Sixth World Symposium on Pulmonary Hypertension (WSPH), recognizes five PH categories listed here sequentially as groups 1–5: PAH; PH due to left heart disease; PH due to chronic lung disease or sleep-disordered breathing; CTEPH; and a group of miscellaneous diseases that rarely (or inconsistently) cause PH (Table 294-1). Pulmonary Arterial Hypertension WSPH group 1 PH, or PAH, involves marked pulmonary arterial precapillary remodeling,

TABLE 294-1 World Symposium on Pulmonary Hypertension Clinical Classification GROUP 1 Pulmonary arterial hypertension (PAH) 1.1 Idiopathic CHAPTER 294 1.1.1 Non-responders at vasoreactivity testing 1.1.2 Acute responders at vasoreactivity testing 1.2 Heritablea 1.3 Associated with drugs and toxinsa 1.4 Associated with: Pulmonary Hypertension 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn GROUP 2 PH associated with left heart disease 2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fractionb 2.2 Valvular heart disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH GROUP 3 PH associated with lung diseases and/or hypoxia 3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed restrictive/obstructive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease (e.g. high altitude) 3.6 Developmental lung disorders GROUP 4 PH associated with pulmonary artery obstructions 4.1

Chronic thrombo-embolic PH 4.2 Other pulmonary artery obstructionsc GROUP 5 PH with unclear and/or multifactorial mechanisms 5.1 Hematological disordersd 5.2 Systemic disorderse 5.3 Metabolic disordersf 5.4 Chronic renal failure with or without hemodialysis 5.5 Pulmonary tumor thrombotic microangiopathy 5.6 Fibrosing mediastinitis Note: Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders. Left ventricular ejection fraction for HF with reduced ejection fraction: ≤40%; for HF with mildly reduced ejection fraction: 41–49%. Other causes of pulmonary artery obstructions include: sarcomas (high or intermediate grade or angiosarcoma), other malignant tumors (e.g., renal carcinoma, uterine carcinoma, germ-cell tumors of the testis), non-malignant tumors (e.g., inherited and acquired chronic hemolytic anemia and chronic myeloproliferative disorders, sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1, glycogen storage diseases and Gaucher disease.) Abbreviations: HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. Source: Reproduced with permission of the © ERS 2024: Eur Resp J 61:2200879, 2023; DOI:10.1183/13993003.00879-2022. including intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and classic plexiform lesions (described in detail above in the Pathobiology section). The hemodynamic criteria for PAH are sustained elevation in resting mPAP >20 mmHg, PVR >2.0 WU, and PAWP or LVEDP of ≤15 mmHg based on RHC. Idiopathic PAH (IPAH) is a progressive disease that leads to right heart failure and early mortality. From the original National Institutes of Health registry on IPAH in 1987, the average age at diagnosis was 36 years, with only 9% of patients with IPAH over the age of 60. However, contemporary data now inclusive of numerous international registries suggest a dif ferent clinical profile. The mean age of PAH patients is reported to be 54–68 years old across studies. This reflects, in part, rising awareness

of this disease in the elderly. The prevalence of IPAH favors women to men by ~3.1-fold; however, the hemodynamics at diagnosis are more severe, and the prognosis is less favorable in men compared to women. Patients with hereditary PAH from a BMPR2 mutation tend to be younger at diagnosis with more severe cardiopulmonary hemodynam ics and are associated with comparatively greater clinical risk compared to IPAH. The rate of conversion to PAH among carriers without clini cal evidence of disease is ~2.3% per year.

PART 6 Disorders of the Cardiovascular System Diseases Associated with PAH Other forms of PAH that deserve specific consideration are those associated with congenital heart dis ease with intracardiac shunt, connective tissue disease, portal hyper tension, and HIV. CONGENITAL HEART DISEASE PAH in the setting of congenital heart disease is important to recognize since surgical correction may be indi cated and when successful is associated with favorable prognosis. This is particularly salient today, as more congenital heart disease patients live to adulthood and populate general medical practices. Still, refer ral to adult congenital heart disease centers should be considered for patients with suspected PAH, which in this population is subclassified into four groups: Eisenmenger's syndrome, systemic-to-pulmonary shunts, coincidental or small defects causing shunts, and postoperative/ closed defects causing shunts. Surgical repair of congenital anatomic lesions may be indicated prior to elevation in PVR >3.0 WU to avoid the development of Eisenmenger's syndrome, a pathophysiologic consequence of progressive pulmonary vascular remodeling due to a large-volume left-to-right shunt that is associated with cyanosis, hyperviscosity, weakness, and shortened life span. Indeed, the effect of changing the PVR threshold to define precapillary PH from 3.0 to 2.0 WU on the timing of shunt repair is an evolving

concept. CONNECTIVE TISSUE DISEASE Patients with connective tissue disease– associated PAH are encountered relatively commonly in clinical prac tice. Although case series link rheumatoid arthritis and systemic lupus erythematosus with pulmonary vascular disease, the predominant clinical phenotype is systemic sclerosis-associated PAH. It is important to distinguish patients with limited cutaneous scleroderma from those with diffuse scleroderma because PH in the former is likely PAH and PH in the latter often occurs in the setting of interstitial lung disease. Although the average age of scleroderma onset is between 30 and 50 years old, patients who eventually develop scleroderma-associated PAH tend to be older at the time of scleroderma diagnosis. The development of PAH in scleroderma is particularly worrisome prog nostically, although implementation of modern therapies improves outcome. Overlap between pulmonary circulatory and interstitial lung disease is encountered commonly in clinical practice. It is tempting to focus on the hemodynamic derangement of these patients as a focal point of clinical care, although the efficacy of implementing PAHspecific treatment to these overlap syndrome patients is unproven. PORTOPULMONARY HYPERTENSION Among patients with estab lished portal hypertension, 2–10% develop portopulmonary hyper tension independent of the cause of liver disease. Furthermore, portopulmonary hypertension is observed in patients with nonhepatic etiologies of portal hypertension. A hyperdynamic circulatory state is common, as in most patients with advanced liver disease; however, the same pulmonary vascular remodeling observed in other forms of PAH is seen in the pulmonary vascular bed in portopulmonary hyperten sion. It is important to distinguish this process from hepatopulmonary syndrome, which can also manifest with dyspnea and hypoxemia but is pathophysiologically distinct from portopulmonary hypertension in that abnormal vasodilation of the pulmonary vasculature leads to intrapulmonary shunting. Portopulmonary hypertension is an estab lished marker of adverse outcome in the post–liver transplant period with 100% mortality reported in one study among patients with mPAP ≥50 mmHg. The optimal preoperative PVR threshold used to predict elevated postoperative risk must also consider morbidity linked to pro longed transplant wait time. At present, PVR >3.0 WU is considered a strong predicter of unfavorable outcome after transplant, although PVR >2.0 WU also appears to capture potential risk.

HIV-PAH The true prevalence of HIV-PAH is not known; however, this PAH subtype is an important cause of mortality in the HIVinfected population, and prognosis in these patients is among the least favorable for all PH subgroups. There is no correlation between the stage of HIV infection and the development of PAH. By contrast, popu lation data from the U.S. Veterans Administration database suggest a positive and inverse correlation, respectively, between CD4+ count and viral load with estimated pulmonary artery systolic pressure (ePASP) on echocardiography. An ePASP >40 mmHg in HIV-infected patients is associated with a 40% increase in all-cause mortality compared to uninfected counterparts. Although delineating patients with PAH from within this cohort and other unselected populations is not possible, there is a pressing need to understand further the role of HIV-PH in prognosis patients, particularly in endemic areas of the world. Pulmonary Hypertension Associated with Left Heart Disease Patients with PH due to left ventricular systolic dysfunc tion, aortic and mitral valve disease, and heart failure with preserved ejection fraction (HFpEF) are classified in WSPH group 2. The hall mark of this PH phenotype is elevated left atrial pressure with resulting pulmonary venous hypertension. In left-sided systolic heart failure or HFpEF, even mildly elevated mPAP is associated with adverse clinical outcome. It should be noted that PH in the setting of mitral stenosis or regurgitation is an indication for surgical (or percutaneous) valve intervention. Recent data suggest that PH is common in obstructive HCM and associated with

fibroproliferative remodeling of distal pul monary arterials even when mPAP is only mildly elevated (Fig. 294-8). In amyloid cardiomyopathy, ~75% of patients have elevated mPAP, and combined pre-/postcapillary PH is the most common hemodynamic subgroup. Regardless of the cause of elevated left atrial pressure, left atrial hypertension causes pulmonary venule sclerosis and thickening that leads to PH and, ultimately, pathogenic changes to pulmonary arterioles.
Pulmonary Hypertension Associated with Lung Disease

Intrinsic lung disease is the second most common cause of PH and has been observed in both chronic obstructive pulmonary disease (COPD) and interstitial lung disease. Additionally, PH is also diagnosed in dis eases of mixed obstructive/restrictive pathophysiology: bronchiectasis, cystic fibrosis, mixed obstructive-restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. When associated with chronic lung disease, PH is usually modest. For example, 90% of COPD patients have mPAP >20 mmHg, but an mPAP >35 mmHg is observed in only 5% of patients. Nonethe less, the subgroup of patients with primary lung disease and severe PH is challenging clinically, as extensive pulmonary arterial involvement, very low DLCO on pulmonary function testing, and inhibition of nor mal vasoreactivity are observed and are associated with poor outcome. Sleep-disordered syndromes generally result in mild PH.
Pulmonary Hypertension Associated with Chronic Throm boembolic Disease The development of PH after chronic throm boembolic obstruction of the pulmonary arteries, termed CTEPH, is well described. The incidence of CTEPH following a single pulmo nary embolic event is difficult to determine accurately, but probably is between 3 and 7% of patients. Importantly, 25% of patients with CTEPH have no history of clinical venous thromboembolism, sug gesting that CTEPH may develop following a subclinical pulmonary embolism or through a diverse range of mechanisms. Obstruction of the proximal pulmonary vasculature due to webbing, stricture, or focal fibrotic occlusion signifies proximal vessel involvement. Distal pulmonary arterioles remodel by luminal narrowing or obliteration. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus (Fig. 294-9). Chronic thromboembolic disease refers to patients with thrombotic pulmonary arterial remodeling and dimin ished exercise capacity with correlative symptoms in the absence of PH. This subtype is less common than CTEPH but requires consider ation in patients with prior PE and dyspnea even if echocardiography is reassuring.

Elastin Trichrome Hematoxylin and Eosin Control HCM HCM FIGURE 294-8 Pulmonary vascular remodeling in patients with obstructive hypertrophic cardiomyopathy (HCM) and mild pulmonary hypertension. Photomicrographs showing pulmonary arterial histopathophenotype of HCM. Paraffin-embedded tissue sections from control donors without lung disease and example autopsy specimens from patients with symptomatic obstructive HCM were analyzed after hematoxylin and eosin, Masson trichrome, and Verhoeff-Van Gieson staining. (Adapted with permission from BA Maron et al: Chest 163:678, 2023.) ■ ■OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE Sarcoidosis Patients with sarcoidosis can develop PH as a result of lung involvement, and those who present with progressive dyspnea and PH require a thorough evaluation. In sarcoidosis, PH develops mainly due to granulomatous inflammation of the pulmonary vessels, although mechanical compression of pulmonary arteries by enlarged lymph nodes is also reported. Sickle Cell Disease Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease (and other hemoglobinopathies), including PH, which occurs in 6–10% of patients. The etiology is multifactorial, including hemolysis, hypoxemia, throm

boembolism, chronically high CO, and chronic liver disease. Schistosomiasis Schistosomiasis affects >230 million people worldwide, of whom 5% develop PAH. Thus, this infection is among the most common causes of PAH worldwide. The development of PAH occurs in the setting of hepatosplenic disease and portal hypertension. Indeed, even in the absence of schistosomiasis, splenectomy is a risk factor for PAH, presumably through impaired platelet sequestration and associated microthrombosis of pulmonary arterioles. Studies suggest that inflammation from a schistosomiasis infection induces pulmonary vascular injury through a combination of the following A B C FIGURE 294-9 Chronic thromboembolic pulmonary hypertension (CTEPH) imaging findings and surgical endarterectomy specimen. A. Contrast-enhanced computed tomography of the chest shows an obstructive vascular pattern involving segmental pulmonary arteries (yellow arrows) in a 63-year-old man with exertional dyspnea and remote history of pulmonary embolism. B. Still image of a pulmonary angiography of the right lung (submaximal injection shown) shows pulmonary artery stricture, webbing, and severe dearborization that is classic for CTEPH. C. Fibrotic, chronic clot specimens resected during surgical pulmonary endarterectomy, which is curative in most CTEPH patients. (Panel C is reproduced with permission from IM Lang, M Madani: Update on chronic thromboembolic pulmonary hypertension. Circulation 130:508, 2014.)

CHAPTER 294 Pulmonary Hypertension mechanisms: luminal obstruction by worm eggs, pulmonary artery endothelial cell inflammation, or portal hypertension that promotes a portopulmonary hypertension-PH phenotype The diagnosis is con firmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PAH in these patients is unknown. ■ ■PHARMACOLOGIC TREATMENT OF PAH There are 14 U.S. Food and Drug Administration (FDA)–approved medical therapies for PAH, and standardized treatment strategies have been developed that emphasize early, aggressive pharmaco therapy initiated at a specialty clinical center. Among optimally treated patients, the 1-, 3-, and 5-year survival estimates are 82, 67, and 58%, respectively, but this may overestimate risk since outcome data in the era of routine dual (and in some cases triple) therapy are lacking. All approved medical therapies target the prostacyclin, NO•, or endothelin receptor signaling pathways. Drug delivery methods now include oral, inhaled, subcutaneous (including via surgically implanted devices), and intravenous routes. Prostanoids In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A2 produc tion. Prostacyclin (PGI2) activates cyclic adenosine monophosphate 1cm

(cAMP)–dependent pathways that mediate vasodilation. PGI2 also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. This imbalance of media tors is offset therapeutically by the administration of either exogenous prostacyclin (and analogues, termed prostanoids) or a prostacyclin receptor agonist.

PART 6 Disorders of the Cardiovascular System Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of epo prostenol in World Health Organization (WHO) Functional Class (FC) III and IV PAH patients was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-MWD, and mortality. Trepro stinil has a longer half-life than epoprostenol (~4 h vs ~6 min), which allows for subcutaneous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and survival in

PAH. Inhaled prostacyclin provides the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects of infusion catheters (e.g., risk of infection and infusion site reactions). Both inhaled iloprost and treprostinil have been approved for patients with PAH and severe heart failure symptoms. Oral prostacyclin is also efficacious in clinical trials, but the maximal dose is modest and, there fore, generally reserved as a second-line therapy. Selexipag is an oral nonprostanoid diphenylpyrazine derivative that binds the prostaglandin I2 (IP) receptor with high affinity. The active metabolite of selexipag has a prolonged half-life in comparison with prostanoid analogues and permits twice-daily dosing. The efficacy of selexipag was evaluated in patients with PAH in New York Heart Association (NYHA) FC II to III on background therapy with either an endothelin-1 (ET-1) receptor antagonist or sildenafil, or both. This trial represents the largest randomized placebo-controlled trial among patients with PAH ever completed, enrolling 1156 patients treated for a median of 1.4 years. Selexipag reduced the risk of hospitalization and the risk of disease progression by 43% ($p < .0001$) compared to those who received placebo. There were no significant differences in mortal ity between the two study groups, and the side effect profile was similar to that of prostacyclins. Endothelin Receptor Antagonists Endothelin receptor antago nists (ERAs) inhibit the detrimental effects of ET-1, a potent endog enous vasoconstrictor and vascular smooth muscle mitogen. In PAH, ET-1 associates positively with PVR and mPAP and inversely with CO and 6-MWD. The ET-1 signaling axis is complex and cell type–specific: ET type A (ETA) and type B (ETB) receptors expressed in pulmonary artery smooth muscle cells mediate vasoconstriction, whereas human pulmonary artery endothelial cells express ETB receptors that promote ET-1 clearance and vasodilation through endothelial nitric oxide synthase activation and prostacyclin release. The three ERAs approved for use in the United States are the non selective ETA/B receptor antagonists bosentan and macitentan and the selective ETA antagonist ambrisentan. Studies have shown that bosen tan improves hemodynamics and exercise capacity and delays clinical worsening. The randomized, placebo-controlled, phase 3 Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 trial comparing bosentan to placebo demonstrated improved symp toms, 6-MWD, and WHO FC in patients treated with bosentan. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) study comparing bosentan to placebo demonstrated improved PVR and 6-MWD in patients with WHO FC II. Several studies, including the phase 3, placebo-controlled Ambris entan in Pulmonary Arterial Hypertension, (ARIES)-1 trial, have demonstrated that ambrisentan improves exercise tolerance, WHO FC, hemodynamics, and quality of life in patients with PAH. More recently, the Study with an Endothelin Receptor Antagonist in Pulmonary Arte rial Hypertension to Improve Clinical Outcome (SERAPHIN) trial randomized 742 PAH patients to receive placebo or macitentan, which is an ETA/B antagonist with optimized receptor binding affinity. The majority of patients were on some form of background PAH therapy. Over an average treatment duration of 85 weeks, the hazard ratio for

achieving the composite primary endpoint of PAH-related clinical worsening, which included death or disease progression, was decreased by 45% in the 10-mg dose arm. Nitric Oxide Pathway Effectors The gaseous, lipophilic mol ecule NO• is generated by endothelial nitric oxide synthase in endo thelial cells and activates soluble guanylyl cyclase (sGC) to generate cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells and platelets. The cyclic nucleotide cGMP is a second messenger that induces vasodilation through relaxation of arterial smooth muscle cells and inhibits platelet activation. Phosphodiesterase type 5 (PDE5) enzymes are highly expressed in lung vascular tissue (and the corpus carvernosum of the penis). The PDE5 inhibitors prevent

hydrolysis (inactivation) of cGMP to maximize NO•-dependent vasodilation, serving as the basis for use of this drug class in the treatment of PH (and erectile dysfunction). The two PDE5 inhibitors used for the treat ment of PAH are sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6-MWD. Riociguat increases bioactive cGMP by (1) stabilizing the molecular interaction between NO• and sGC, and (2) directly stimulating sGC independent of NO• bioavailability. Riociguat significantly improved exercise capacity, pulmonary hemodynamics, WHO FC, and time to clinical worsening in patients with PAH and is the sole approved pharmacotherapy for CTEPH patients for whom surgical pulmonary endarterectomy is ineffective or contraindicated. Activin Signal Inhibitor Therapy Motivated by basic and trans lational data suggesting that treatment with a TGF-β ligand trap inhib its the proproliferative activity of activin ligands in pulmonary vascular cells, sotatercept was developed as a novel fusion protein of the Fc domain of human IgG and the extracellular domain of activin receptor type II. Sotatercept blocks activin receptor II–ALK 4/5/7 signal trans duction to upregulate BMPR2 bioactivity. The putative effect of this drug's reaction in PAH is rebalancing of the TGF-β–BMPR2 pathway to restore normal cellular survival and growth patterns. The PULSAR trial was a large, phase 2, placebo-controlled trial demonstrating a dose-dependent decrease in PVR by sotatercept (0.3 and 0.7 mg/kg administered as an injection) at study week 24 compared to baseline of –1.8 WU and 3.0 WU, respectively. The STELLAR trial was a phase 3 placebo-controlled trial that studied the effect of sotatercept 0.3 mg/kg with target dose of 0.7 mg/kg on 6-MWD. The patients in the study had moderate or severe symptom burden despite ongoing pulmonary vasodilator treatment. In fact, ~60% of patients were on triple therapy, including 40% who were on treatment with intravenous prostacyclin treatment, typically reserved for high-risk or very-highrisk patients (see below). Despite this prior treatment, sotatercept therapy resulted in an average of +40 m improvement in 6-MWD compared to –1.4 m for placebo and was associated with significant improvement in nearly all secondary endpoints including WHO FC improvement, reduction in NT-proBNP level, and shorter time to death or PAH worsening. Telangiectasia development was observed in 10.4% of patients in the sotatercept group, which tracks with the angio proliferative bioactivity reported for TGF-β, although the clinical rel evance of these vascular anomalies is not known. Finally, the long-term open-label study that tracked clinical progress up to 1 year in patients from PULSAR demonstrated a sustained (but not progressive) benefit in PVR reduction by sotatercept without an unexpected change in the proportion of side effects given the duration of the follow-up period. ■ ■APPROACH TO PAH TREATMENT Treatment aims to achieve a low clinical risk profile, defined as a 1-year mortality risk of <5%. Generally, this describes a patient with mini mal symptoms, WHO FC I or II, 6-WMD >440 m, and cardiac index ≥2.5 L/min per m2. To accomplish this goal, early referral to an expert center is advised since most patients will ultimately require two or more PAH pharmacotherapies in addition to risk factor modification (such as a low-sodium diet), diuretic use to include mineralocorticoid receptor antagonists if tolerated, supplemental oxygen, and prescrip tion (or supervised) exercise (Fig. 294-10). It is clear that targeting the diverse pathobiologic and pathophysiologic events involved in vascular

Unexplained Dyspnea or Suspected PH Fast Track Referral: -PAH -CTEPH -Warning Signs General Practitioner -Medical History -Physical Examination -ECG -BNP/NT-pro-BNP O2 Saturation Suspected Cause Lung Disease PH or Cardiac Disease Lung Assessment -PFT -ABG -Chest XR -Chest CT -CPET Rapid CrossReferral as Needed Low Causes other than PH Identified? No Mange Accordingly Further Work up Suspect PAH or CTEPH Refer to PH Center FIGURE 294-10 Strategy for diagnosing pulmonary hypertension (PH) in clinical practice. Diagnostic algorithm of patients with unexplained

dyspnea and/or suspected pulmonary hypertension. ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PFT, pulmonary function tests; PH, pulmonary hypertension. Warning signs include rapid progression of symptoms, severely reduced exercise capacity, presyncope or syncope on mild exertion, and signs of right heart failure. Lung and heart assessment by specialist as per local practice. CT pulmonary angiography recommended if PH suspected. Includes connective tissue disease (especially systemic sclerosis), portal hypertension, HIV infection, and family history of PAH. (Reproduced with permission of the © ERS 2024: Eur Resp J 61:2200879, 2023; DOI:10.1183/13993003.00879-2022.) remodeling is needed to optimize treatment. The concept of combina tion therapy in PAH is modeled after other complex diseases in which a similar approach has been effective, including HIV, cancer, and left heart failure. The approach to therapy in a patient with incident PAH is outlined in Fig. 294-11. The role of early, aggressive therapy with combination oral treatments was addressed in the landmark Initial Use of Ambrisen tan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION) trial. Treatment-naïve, incident PAH patients (n = 500) were ran domized to a combination of ambrisentan and tadalafil, ambrisentan monotherapy, or tadalafil monotherapy. Up-front combination therapy with ambrisentan and tadalafil was associated with a 50% lower risk of clinical worsening (composite of death, lung transplantation, hospital ization for PAH worsening, and worsening PAH) when compared with the monotherapy groups. This difference was driven primarily by the delay in time to first hospitalization. Importantly, initial combination therapy was not associated with an increase in adverse events. Registry data suggest that patients on dual therapy with a PDE5 inhibitor plus ERA combinations alternative to the drugs studied in AMBITION also have better outcomes compared to patients treated with monotherapy, suggesting that the attendant benefit from combination therapy may not be drug specific. The paradigm shift toward early, aggressive pharmacotherapy in PAH is expanding to up-front triple combination therapy. Clinical

CHAPTER 294 Pulmonary Hypertension Heart Assessment -Echocardiography -CPET Intermediate or High PH probability studies on up-front triple therapy remain mixed, which is likely driven by challenges surrounding patient selection given the precarious bal ance between cumulative off-target effects occurring when multiple vasoactive drugs are initiated at the same time, frailty and limited hemodynamic reserve associated with advanced PAH, and need for aggressive treatment to mitigate severely abnormal hemodynamics or right ventricular heart failure. Generally, treatment deescalation, esca lation, or class switching for patients with established PAH should be decided in partnership with a PAH clinical center of excellence. Treatment of HFpEF Disease-specific treatments for HFpEF-PH are lacking. The focus of care should be to optimize contemporary treatment of HFpEF, including minimizing excessive salt and fluid intake while advancing SGLT-2 therapy, mineralocorticoid therapy, and diuretics, and encouraging regular exercise to promote weight loss and conditioning. Invasive PA pressure monitoring may be helpful for tracking elevation in LVEDP, detected as PH, to avert hospitalization. Treatment of PH due to Lung Disease Inhaled iloprost improved 6-MWD on average +33 m in a placebo-controlled random ized clinical trial studying patients with interstitial lung disease and PH and moderate-to-severe exercise limitation. Although a promising future strategy for the routine management of patients, additional data are needed to confirm efficacy and clarify the criteria defining optimal patients for treatment since dosing is frequent and a substantial rate

Incident PAH Patient Non-Vasoreactive With chest pain, syncope, WHO FC IV or other high risk findings1 Vasoreactive Without chest pain, syncope, WHO FC IV or other high risk findings1 PART 6 Disorders of the Cardiovascular System Initial Therapy Initial Therapy Oral Calcium Channel Antagonist Therapy i.v. or s.c. Prostacyclin + Ambrisentan + Tadalafil Ambrisentan + Tadalafil or Macitentan + Tadalafil 1pVO2 <11 mL/kg/min; NT-pro-BNP >1100 ng/mL; at least moderate pericardial effusion; cardiac index <2.0 L/min/m2, PVR ≥12 WU. FIGURE 294-11 Treatment strategy overview for patients with newly diagnosed pulmonary arterial hypertension (PAH). Newly diagnosed patients with idiopathic, hereditary, or drug-induced PAH should be considered for vasoreactivity testing in the cardiac catheterization laboratory at an expert pulmonary hypertension center. In the absence of a high-risk clinical profile, patients who demonstrate a positive vasoreactivity response, defined by decrease in mean pulmonary artery pressure ≥10 mmHg from baseline to ≤40 mmHg without a decrease in cardiac output, should be initiated on calcium channel antagonist therapy dose titrated to optimal clinical benefit/ adverse effect balance. For patients with PAH without evidence of vasoreactivity but with high-risk findings, consideration of up-front therapy with the prostacyclin analogue treprostinil administered by intravenous (IV) or subcutaneous (SC) route plus the phosphodiesterase type 5 inhibitor tadalafil and endothelin receptor antagonist ambrisentan is indicated. For patients with PAH without vasoreactivity or high-risk findings, initial combination therapy with tadalafil and ambrisentan or the alternate endothelin receptor antagonist macitentan should be considered. NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO2, peak volume of oxygen consumption; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization Functional Class; WU, Wood units. (Reproduced with permission from BA Maron: Revised definition of pulmonary hypertension and approach to management: A clinical primer. J Am Heart Assoc 12:e029024, 2023.) of treatment attrition is notable. It is also unclear if inhaled iloprost is generalizable to other lung-PH phenotypes, as at least one study focus ing on COPD-PH was terminated early, presumably owing to a lack of benefit or adverse effects. Treatment of CTEPH Pulmonary endarterectomy performed at a high-volume surgical referral center is the preferred therapy in patients with favorable anatomy and profile. Distal fibrothrombotic remodel ing, PVR >12 WU, right heart failure, and NYHA FC IV are viewed Assessment by Multi-disciplinary CTEPH Expert Team PH Clinician Chest Radiologist Thoracic Surgery Interventional Cardiology Proximal vs. distal clot Comorbidities PVR >12 WU Right heart failure NYHA FC IV Pulmonary Endarterectomy: Operable Pulmonary Endarterectomy FIGURE 294-12 Algorithm for the management of chronic thromboembolic pulmonary hypertension (CTEPH). BPA, balloon pulmonary angioplasty; NYHA FC, New York Heart Association functional class; PH, pulmonary hypertension; PVR, pulmonary vascular resistance. (Adapted from NH Kim et al: Eur Respir J 53:1801915, 2019.)

Non-Vasoreactive Without chest pain, syncope, WHO FC IV or other high risk findings1 Initial Therapy as high-risk findings and may be prohibitive in terms of postoperative risk. Patients who are ineligible for pulmonary endarterectomy or do not experience a complete clinical result in the postoperative phase should be considered for treatment with riociguat (sGC stimulator) therapy, balloon pulmonary angioplasty (BPA), or a combination of both. Compared to riociguat, BPA modulates a decrease in mPAP of –9.3 mmHg but requires on average five procedural attempts and is associated with some important potential complications, including hemoptysis and reperfusion pulmonary edema (Fig. 294-12). CTEPH Diagnosis Lifelong Anticoagulation (warfarin preferred) Pulmonary Endarterectomy: Non-Operable Riociguat (sildenafil, treprostinil) ± BPA Refractory Symptoms + PH

TABLE 294-2 FDA-Approved Therapies for the Treatment of Pulmonary Arterial Hypertension (PAH) ROUTE OF ADMINISTRATION DRUG CLASS INDICATION GENERIC NAME Epoprostenol IV Prostacyclin derivative Treatment of PAH to improve exercise capacity Iloprost Inhaled Prostacyclin derivative Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration Treprostinil IV or SC Prostacyclin derivative Treatment of PAH to diminish symptoms associated with exercise Treprostinil Inhaled Prostacyclin derivative Treatment of PAH to improve exercise ability Treprostinil Oral Prostacyclin derivative Treatment of PAH to improve exercise ability Selexipag Oral Selective IP receptor agonist Treatment of PAH to improve a composite endpoint lack of clinical deterioration Bosentan Oral Endothelin receptor antagonist Treatment of PAH to improve exercise capacity and to decrease clinical worsening Ambrisentan Oral Endothelin receptor antagonist Treatment of PAH to improve exercise capacity and delay clinical worsening Macitentan Oral Endothelin receptor antagonist Treatment of PAH to improve a composite endpoint of delay of clinical worsening Sildenafil Oral or IV PDE5 inhibitor Treatment of PAH to improve exercise capacity and delay clinical worsening Tadalafil Oral PDE5 inhibitor Treatment of PAH to improve exercise ability Riociguat Oral Soluble guanylyl cyclase stimulator Treatment of PAH to improve exercise ability Abbreviations: FDA, U.S. Food and Drug Administration; IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase-5; SC, subcutaneous. ■ ■UNMET AND FUTURE RESEARCH NEEDS IN PULMONARY HYPERTENSION Delayed diagnosis is a major barrier to improving outcome in PAH. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. At-risk patients should be referred early to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art (multidisciplinary) care. In addition, the role of currently available drugs in early-stage disease is not known and requires further investigation (Table 294-2). The anticipated approval of sotatercept is exciting and paves a path toward the availability of the first novel drug class in PAH in nearly two decades. However, clinical trial data continue to lack information from diverse patient subgroups, suggesting that health inequity in PH remains a critical opportunity for progress. ■ ■FURTHER READING Alba GA et al: NEDD9 is a novel and modifiable mediator of plateletendothelial adhesion in the pulmonary circulation. Am J Respir Crit Care Med 203:1533, 2021. Bernardo RJ et al: Health care disparities in pulmonary arterial hypertension. Clin Chest Med 44:543, 2023.

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