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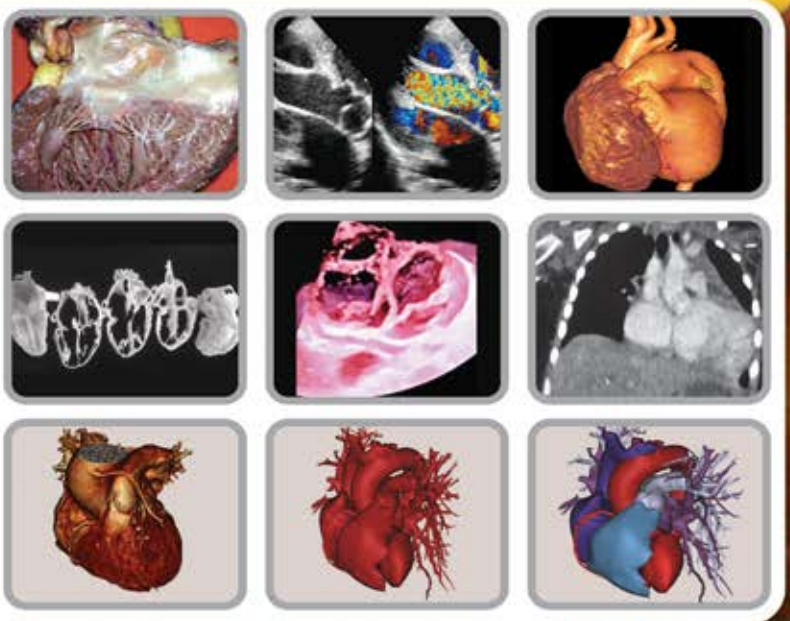
A Comprehensive Approach to CONGENITAL HEART DISEASES

SECOND EDITION





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Reema Chugh

Foreword
Joseph K Perloff

JAYPEE

A Comprehensive Approach to

CONGENITAL HEART DISEASES

Second Edition

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Chapter

65 Pulmonary Hypertension

Maddury Jyotsna, Madhavapeddi Aditya

Yet, there is already plenty of evidence to show that we are in much danger of losing our clinical heritage and of pinning too much faith in figures thrown up by machines. Medicine must suffer if this tendency is not checked.

—Paul Wood

INTRODUCTION

The lung has a unique double arterial blood supply from the pulmonary and bronchial arteries, as well as double venous drainage into the pulmonary and azygos veins.[1] The pulmonary circulation is characterized by high flow [the entire right ventricular (RV) output] and by low pressure and low resistance. Its wide and thin-walled vessels reflect these hemodynamic features. The normal pulmonary vascular bed offers less than one-tenth the resistance to flow offered by the systemic bed. The calculated pulmonary vascular resistance (PVR) in normal adults is 67 ± 23 dynes-sec·cm^{-5} or 1 Wood unit. Although it has been called the "lesser circulation", the response of the pulmonary vascular bed to a variety of conditions and disease states is the major determinant of clinical outcome.

DEFINITION

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) greater than 25 mm Hg at rest.[2] A mean PAP of 8–20 mm Hg at rest is considered normal, while a mean PAP of 21–24 mm Hg at rest has uncertain clinical implications. Two definitions that were previously accepted are no longer used. They include a mean PAP greater than 30 mm Hg with exercise (measured by right heart catheterization)[3] and a systolic PAP greater than 40 mm Hg (measured by Doppler echocardiography).[4]

Pulmonary hypertension may be secondary to heart defects or lung parenchymal or vascular disease or thromboembolism or idiopathic or combination of these. Because the causes of PH are so diverse, it is essential that the etiology underlying the PH be clearly determined before embarking on treatment.

CLASSIFICATION OF PULMONARY HYPERTENSION

In 1998, a classification for PH was developed at the World Symposium on Pulmonary Hypertension, cosponsored by the World Health Organization (WHO) and later modifications to this classification have been proposed[5,6] (Flowchart 65.1 and Fig. 65.1).

A patient can have PH from the standpoint of an elevated PAP but with normal PVR. There are patients whose resting hemodynamics are normal, but in whom marked elevations in PAP occur with exercise. Hence, a functional classification patterned after the New York Heart Association (NYHA) for heart disease has been developed to allow comparisons of patients with respect to the clinical severity of the disease process (Table 65.1).

MECHANISM OF DEVELOPMENT OF PULMONARY HYPERTENSION

Morphological abnormalities in each cell line of the pulmonary vasculature have been described in cases of idiopathic pulmonary arterial hypertension (IPAH).[7] The vascular changes from pulmonary arterial hypertension (PAH) occur across a spectrum and are likely to be influenced by genetic and environmental factors. The exact cause is unknown, but it probably represents the clinical expression of PAH as the final common pathway from multiple biological abnormalities within the pulmonary circulation.[8-11] Causative factors for PAH development are

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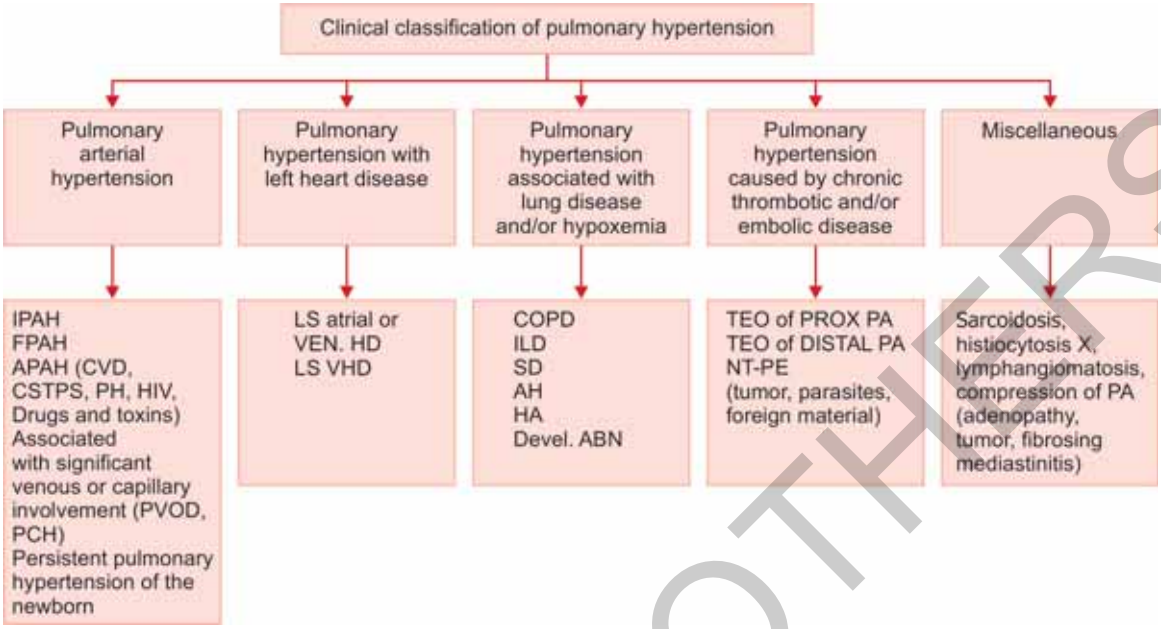
Flowchart 65.1: Revised clinical classification of pulmonary hypertension.



(AH, alveolar hypoventilation; APAH, associated with pulmonary arterial hypertension; COPD, chronic obstructive pulmonary disease; CVD, collagen vascular disease; CSTPS, congenital systemic-to-pulmonary shunts; Devel. ABN, developmental abnormalities; DISTAL PA, distal pulmonary arteries; FPAH, familial pulmonary arterial hypertension; HA, high altitude; HIV, human immunodeficiency virus infection; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; LS, left-sided; NT-PE, nonthrombotic pulmonary embolism; OTHERS, thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy; PCH, pulmonary capillary hemangiomatosis; PH, portal hypertension; PROX PA, proximal pulmonary arteries; PVOD, pulmonary veno-occlusive disease; SD, sleep-disordered breathing; TEO, thromboembolic obstruction; VEN.HD, ventricular heart disease; VHD, valvular heart disease).

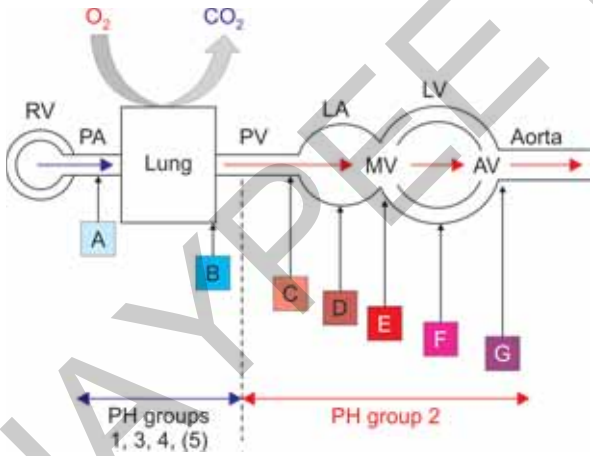


Fig. 65.1: Schematic diagram of various groups of pulmonary arterial hypertension (PH).[6]
(AV, aortic valve; LA, left atrium; LV, left ventricle; MA, mitral valve; RA, right atrium; RV, right ventricle). *Source:* Maeder MT et al. (2017).

dysfunctional endothelium, change in local hemodynamics, defects in ion channels, increased plasma levels of serotonin and elastolytic enzymes, and other vascular proteins. Endothelial cell dysfunction plays major role in pathogenesis of PAH[12] (Flowchart 65.2).

Table 65.1: World Health Organization functional classification of pulmonary hypertension.[7]

Functional class	*Description*
I	Patients with pulmonary hypertension, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near-syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

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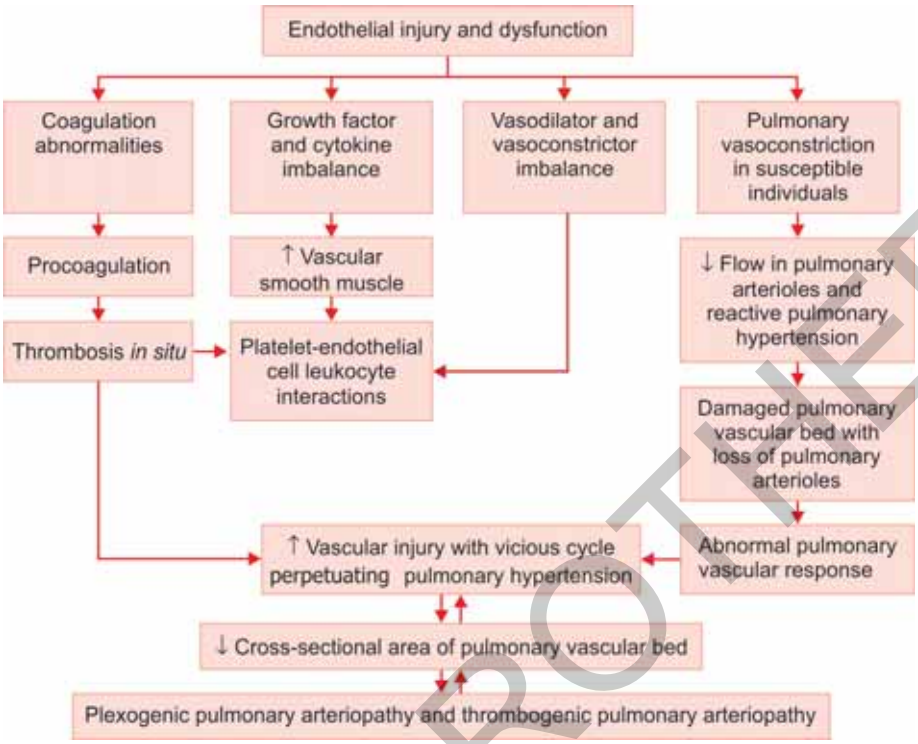
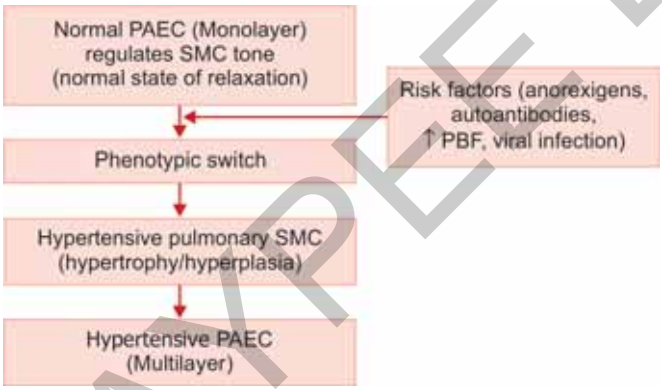
Flowchart 65.2: Major role of endothelial injury in pulmonary arterial hypertension (PAH) pathophysiology.



Flowchart 65.3: Probable pathways causing changes in pulmonary endothelial and smooth muscle cells.



(PAEC, pulmonary artery endothelial cell; PBF, pulmonary blood flow; SMC, smooth muscle cell).

Probable pathways leading to hypertensive pulmonary endothelial and smooth muscle cell changes are represented in Flowchart 65.3. Due to reduced expression of the endothelial isoform of nitric oxide (NO) synthase and expression of different growth factors by dysfunctional endothelial cell, intimal hyperplasia and medial hypertrophy occurs which, in turn, causes PAH (Flowchart 65.4). Equally important factor for PAH development is the in situ thrombosis formation in the small pulmonary arteries due to imbalance between the thrombotic and prothrombotic factors (Fig. 65.2).

Increase in pulmonary flow and shear stress, as in the case of congenital shunt lesions, causes changes in the local hemodynamics, can influence the pulmonary vascular remodeling. Increase in flow causes release of mediators from endothelial cells for induction of vascular smooth muscle cell growth. Increase in shear stress induces apoptosis of endothelial cells. Genetic or acquired defect in potassium and L-type calcium channels, which are important in regulating pulmonary vascular tone are reported in PAH patients.[13] The abnormality in platelet serotonin and mutations in the serotonin transporter and 5-hydroxytryptamine 2B (5-HT_{2B}) receptor have now been reported in patients with IPAH[14,15] (Flowchart 65.5). There is degradation of elastin in small pulmonary arteries from the increased activity of serine elastase (Flowchart 65.6). Increased plasma levels of adrenomedullin and vasoactive intestinal peptide occur in PAH and hypoxic PH.[16,17]

All these causative factors in the presence of susceptible individual (underlying genetic predisposition) cause vicious cycle of PAH development (Fig. 65.3). The PAP response to hypoxia is particularly high in individuals with blood group A. Presumably, a genetic basis underlies these differences in pulmonary vascular reactivity, just as there appears to be

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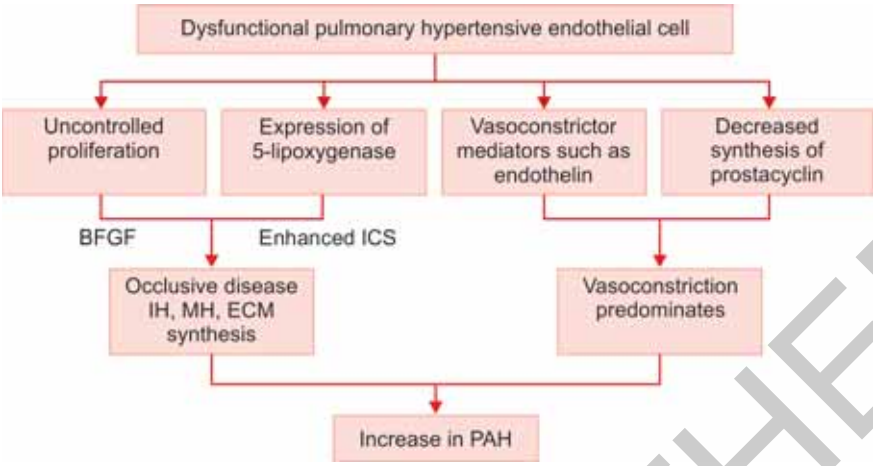
Flowchart 65.4: Mechanism of action of dysfunctional endothelial cell in production of pulmonary arterial hypertension (PAH).



(BFGF, basic fibroblast growth factor; ECM, extracellular matrix; ICS, intracellular signaling; IH, intimal hyperplasia; MH, medial hypertrophy).

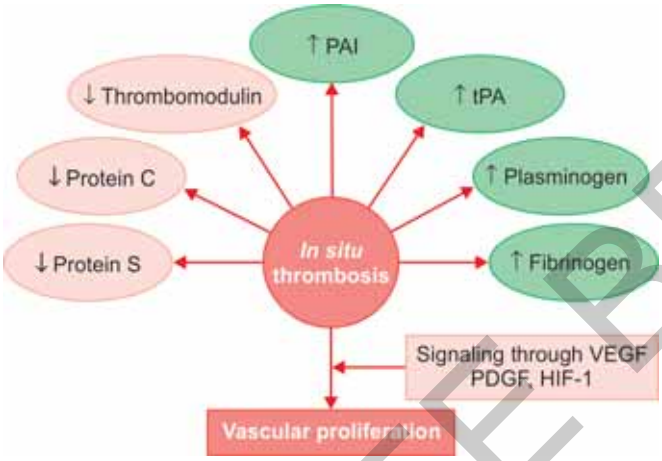
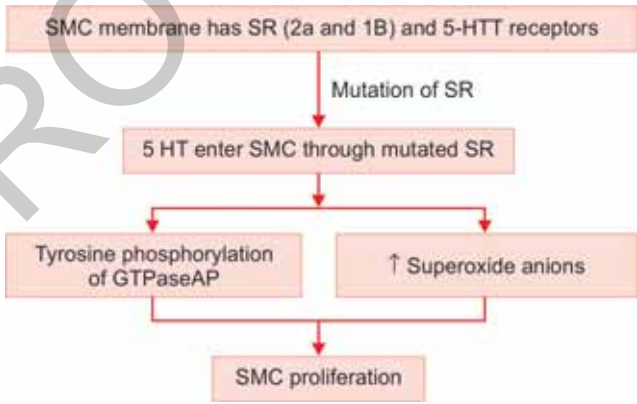


Fig. 65.2: Factors predisposing for in situ thrombosis during the development of pulmonary arterial hypertension.
(HIF-1, hypoxia-inducible factor-1; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor).

Flowchart 65.5: Mechanism of pulmonary smooth muscle cell proliferation by mutated serotonin receptors and transporters in IPAH.



(5-HT, 5-hydroxytryptamine; 5-HTT, 5-hydroxytryptamine transporter; GTPaseAP, guanosine triphosphatase activating protein; SMC, smooth muscle cell; SR, serotonin receptor).

a genetic basis for the increased reactivity of the systemic vascular bed in essential systemic hypertension.

Using linkage analysis, the locus designated PPH-1 on chromosome 2q33 led to the discovery of the *PPH-1* gene. Impaired transforming growth factor beta signaling is found in PAH.[18,19] The bone morphogenetic protein receptor type 2 gene (*BMPR-2*) codes for a receptor member of the TGF-β family. *BMPR-2* modulates vascular cell growth by activating the intracellular pathways (Flowchart 65.7). Other genetic abnormalities found in PAH patient are over expression of serotonin transporter and defects in a common vascular signaling pathway involving angiopoetin-1 (Flowchart 65.8).

PATHOLOGICAL FEATURES

Endothelial cell proliferation, smooth muscle cell hypertrophy, and increased connective tissue and extracellular matrix are found in the large muscular and elastic arteries. In the subendothelial layer, increased thickness may be the result of recruitment and/or proliferation of smooth muscle-like cells. Heath and Edwards classified the pulmonary vascular changes in PAH[20] as given below:

- Grade I: Medial hypertrophy: reversible
- Grade II: Cellular intimal proliferation in an abnormal muscular artery: reversible
- Grade III: Occlusive changes: partially reversible

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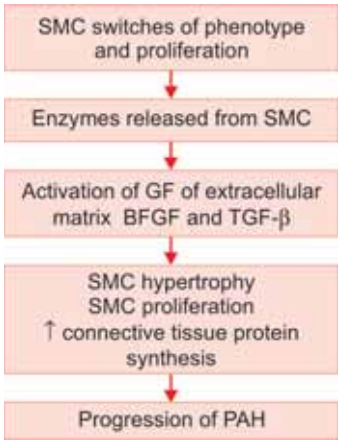
Flowchart 65.6: Role of elastolytic enzymes in progression of pulmonary arterial hypertension (PAH).



(BFGF, basic fibroblast growth factor; SMC, smooth muscle cell; TGF-β, transforming growth factor-beta).

- Grade IV: Vessel dilatation: irreversible
- Grade V: Plexiform lesion: irreversible
- Grade VI: Acute necrotizing arteritis: irreversible

Structural Features Quantified in Congenital Heart Defects[21]

In their study, Haworth et al. demonstrated and explained differences in the appearance of the peripheral pulmonary arteries in different types of congenital heart defect (CHD), which help to interpret the findings of lung biopsies.

- Decreased artery size in ventricular septal defect (VSD), tetralogy of Fallot (TOF), pulmonary atresia. Normal size in hypoplastic left heart, total anomalous pulmonary venous connection (TAPVC).

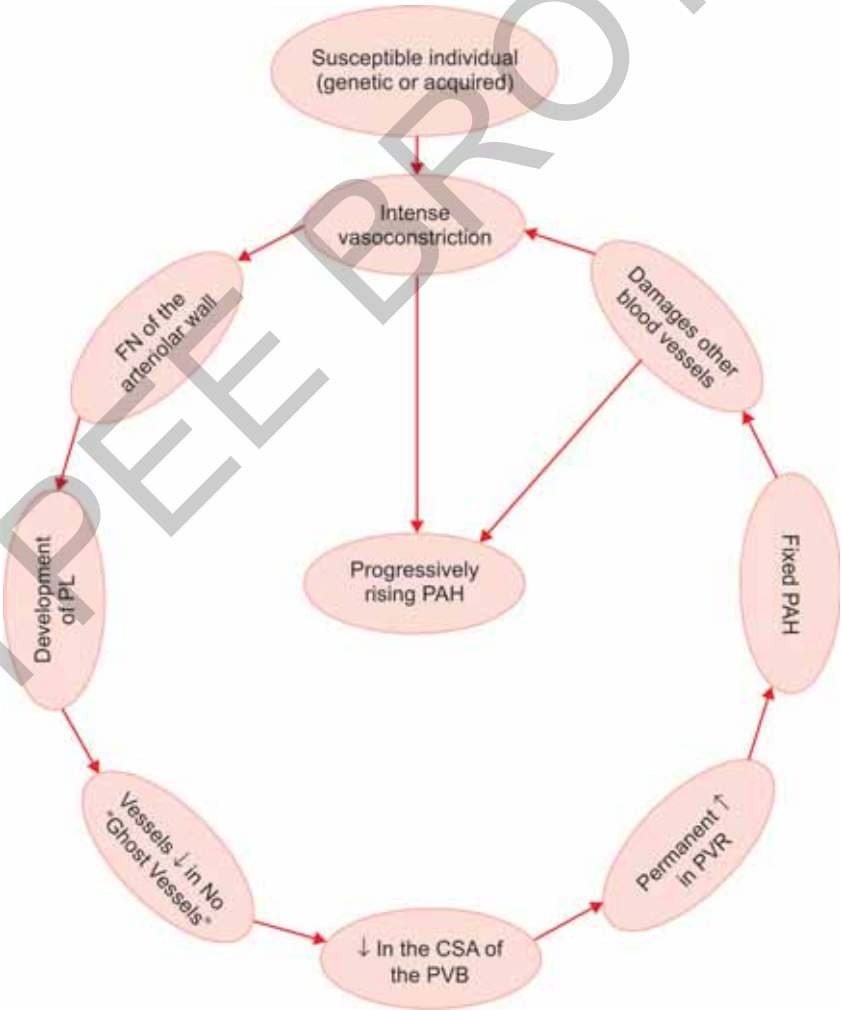


Fig. 65.3: Vicious cycle of PAH development.

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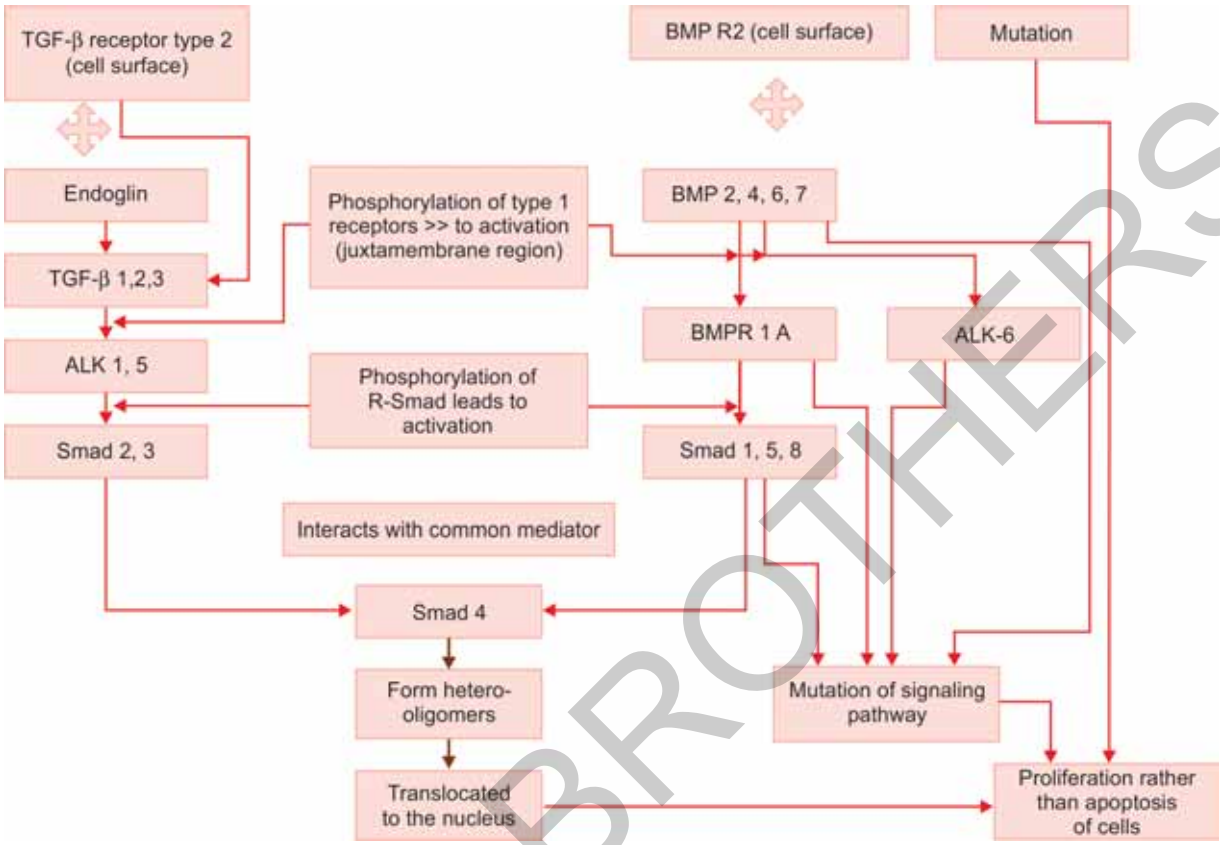
Flowchart 65.7: Intracellular pathways modulated by bone morphogenetic protein receptor type 2 gene (BMPR-2).



- Decreased artery number in VSD, pulmonary atresia. Normal number in TAPVC, TOF. Increased number in hypoplastic left heart, TOF
- Extension of the muscle into peripheral arteries is seen in VSD, hypoplastic left heart, TAPVC
- Increased medial wall thickness.

The most common vascular changes in PAH can best be characterized as a hypertensive pulmonary arteriopathy, which is present in 85% of cases and in the rest it is thrombotic pulmonary arteriopathy. Histopathologically, hypertensive pulmonary vascular disease may involve arteries, veins, or capillaries (arteriopathy, venopathy, and microangiopathy, respectively).[22] Arteriopathy may be isolated medial hypertrophy, plexogenic pulmonary arteriopathy, thrombotic pulmonary arteriopathy, and isolated pulmonary arteritis. Venopathy or pulmonary veno-occlusive disease occurs due to eccentric intimal fibrosis and recanalized thrombi within diseased pulmonary veins and venules. In microangiopathy, pulmonary capillaries throughout the pulmonary parenchyma are infiltrated. In thrombotic pulmonary arteriopathy, typical features include medial hypertrophy of the arteries and arterioles, with both eccentric and concentric nonlaminar intimal fibrosis and the presence of colander lesions, which represent recanalized thrombi.

CLINICAL FEATURES IN PULMONARY ARTERIAL HYPERTENSION

History

Detailed history of the patient is a paramount step for diagnosis, for finding etiology and planning for the management of suspected PH.[23] In most patients, it is an insidious presentation with exercise-induced dyspnea which is progressive over few years. Angina is also a common symptom, occurs late in the disease, may be due to RV ischemia in a hypertrophied right ventricle. As the cardiac output becomes fixed, patient may develop syncope or near-syncope. Once right ventricle fails, signs and symptoms of systemic congestion manifest. Patients rarely develop orthopnea and paroxysmal nocturnal dyspnea late in the

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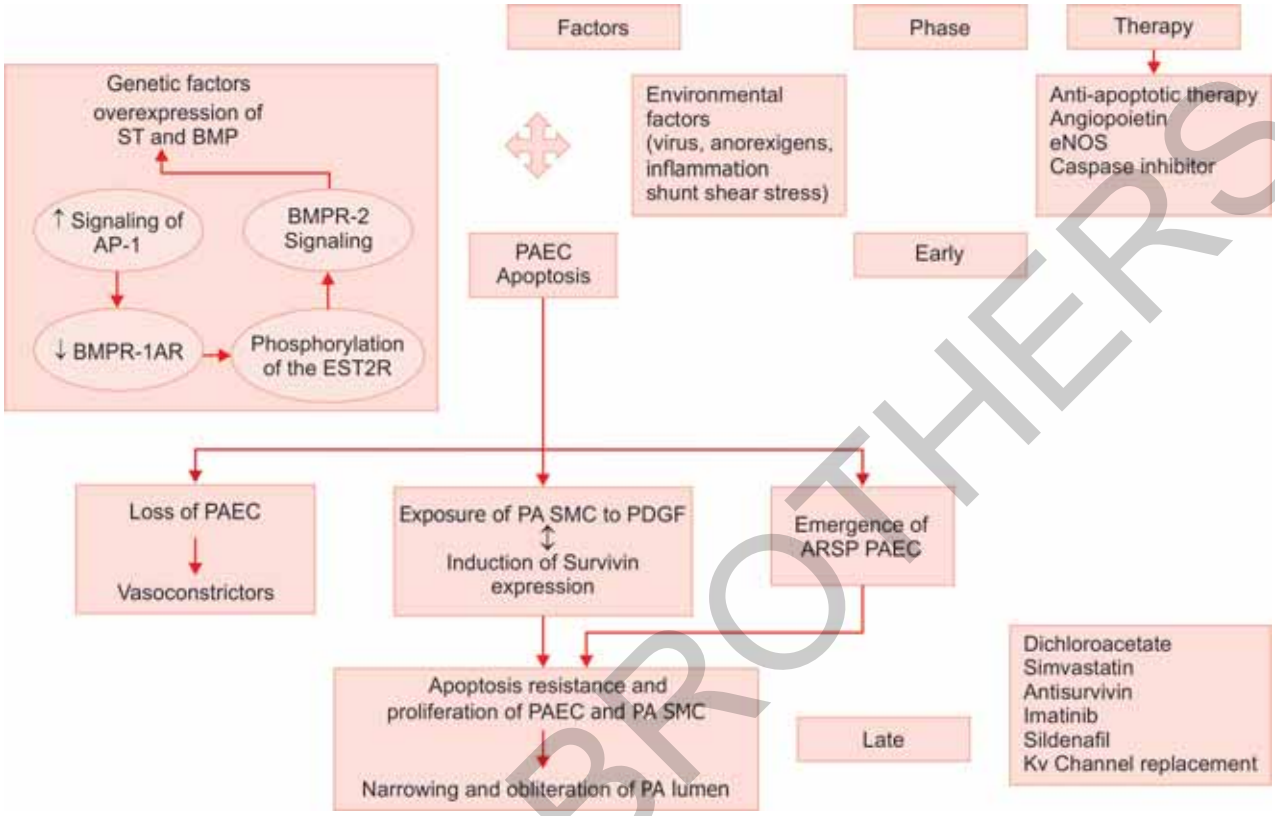
Flowchart 65.8: Probable mechanism of action of genetic and environmental factors in generation of pulmonary arterial hypertension (PAH) at different phases of PAH with probable therapy.



(AP-1, angiopoietin-1; ARSP, apoptosis resistant surviving positive; BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; EST2R, endothelial-specific tie-2 receptor; PA, pulmonary artery; PAEC, pulmonary arterial endothelial cell; PDGF, platelet-derived growth factor; ST, serotonin transporter).

disease process secondary to left ventricular diastolic dysfunction. Chronic cough may be predominant symptom in patients with PH secondary to lung pathology. Hemoptysis is relatively uncommon in patients with PH and may be associated with underlying thromboembolism and pulmonary infarction or in some patients with advanced mitral stenosis. Occasionally hoarseness of the voice may occur due to compression or paralysis of left laryngeal nerve by the dilated pulmonary artery. The systemic disorders which are likely to be associated with PH, should be detected. In most of the patients with congenital heart disease, there is a known history, but patients with atrial septal defects usually manifest later. These patients may have cyanosis which worsens with exercise.

Physical Examination

Cardiovascular findings consistent with PH and RV pressure overload include a large "a" wave in the jugular venous pulse, a low-volume carotid arterial pulse with normal upstroke, a left parasternal (RV) heave, a systolic pulsation produced by a dilated, tense pulmonary artery in the second left interspace, a vascular ejection click and flow murmur in the same area, a closely split second heart sound with a loud pulmonic component, and a fourth heart sound of RV origin. Late in the course, signs of RV failure (e.g. hepatomegaly, peripheral edema, and ascites) may be present. Patients with severe PH may also have prominent "v" waves in the jugular venous pulse as a result of tricuspid regurgitation, a third heart sound of RV origin, a high-pitched early diastolic murmur of pulmonic regurgitation, and a holosystolic murmur of tricuspid regurgitation. Tricuspid regurgitation is a reflection of RV dilation. Cyanosis is a late finding and usually attributable to a markedly reduced cardiac output, with systemic vasoconstriction and ventilation-perfusion mismatch in the lung and rarely due to right-to-left shunting across the stretched patent foramen ovale.

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INVESTIGATIONS

A number of tests are available for the assessment of PAH.[24]

Laboratory Tests

Hemogram may detect polycythemia secondary to chronic hypoxia of lung pathology or right-to-left shunt in congenital heart disease. Tests to detect hypercoagulable state, abnormalities of platelet function, and/or defects in fibrinolysis should be done in appropriate patient. Abnormal liver function test results can indicate RV failure, with resultant systemic venous hypertension. Brain natriuretic peptide (BNP) levels are elevated in patients with PH and correlate positively with the PAP.[24] Uric acid levels are elevated in patients with PH and correlate with hemodynamics. There is an increased incidence of thyroid disease in patients with PAH.[25]

Chest Radiography

The anterior-posterior chest roentgenogram may show the main and branch pulmonary artery dilatation with marked tapering of the peripheral arteries, dilatation of right atrium, with or without lung parenchymal pathology or oligemia. Lateral chest X-ray more specifically detects the RV enlargement. Enlargement of the central pulmonary arteries reflects level of PAP and duration.

Electrocardiography

Right atrial (RA) enlargement and RV hypertrophy may be present. Right axis deviation and precordial T-wave abnormalities are early signs. Left atrial enlargement may be detected in secondary PAH due to left heart disease (LHD). These electrocardiographic abnormalities are usually less pronounced in patients with chronic obstructive pulmonary disease (COPD) than in patients with other forms of PH because of the relatively modest degree of PH that occurs and because of the effects of hyperinflation.

Echocardiography

In PAH, echocardiography plays a major role in detection, assessing the severity and follow-up of PAH. It is also important in detecting the congenital and LHDs producing PH. In thromboembolic pulmonary hypertensive patients, direct visualization of the thrombus in the main and major pulmonary artery branches can be done.

The parameters to be performed and reported in PAH should include a measure of the RV size, RA size, RV systolic function, fractional area change (FAC), tissue Doppler–derived tricuspid lateral annular systolic velocity (S') and longitudinal strain and strain rate, tricuspid annular plane systolic excursion (TAPSE), RV index of myocardial performance (RIMP), systolic pulmonary artery pressure (SPAP), pulmonary artery diastolic pressure (PADP), an assessment of RV diastolic function, and PVR estimation.[26] In advanced cases of PAH, even left ventricular diastolic and systolic function should be assessed. In PAH, RA and RV dilatation with hypertrophy occurs. Diameter more than 42 mm at the base and more than 35 mm at the mid-level indicates RV dilatation. Similarly, longitudinal dimension more than 86 mm indicates RV enlargement. Thickness more than 5 mm indicates RV hypertrophy (RVH). RA area more than 18 cm^2, RA length (referred to as the major dimension) more than 53 mm, and RA diameter (otherwise known as the minor dimension) more than 44 mm at end diastole indicates RA enlargement. RIMP more than 0.40 by pulsed Doppler and more than 0.55 by tissue Doppler indicates RV dysfunction. TAPSE less than 16 mm indicates RV systolic dysfunction (Figs. 65.4A to D). Two-dimensional FAC more than 35% indicates RV systolic dysfunction. To grade the diastolic dysfunction of RV, pulse wave and tissue Doppler interrogation should be done. A tricuspid E/A ratio less than 0.8 suggests impaired relaxation, a tricuspid E/A ratio of 0.8–2.1 with an E/e ratio more than 6 or diastolic flow predominance in the hepatic veins suggests pseudonormal filling and a tricuspid E/A ratio more than 2.1 with deceleration time less than 120 ms suggests restrictive filling. With the tricuspid regurgitation peak velocity, using Bernoulli equation ($4v^2$), we can calculate the RV systolic pressure which, in turn, reflects the SPAP in the absence of RV outflow tract (RVOT) obstruction. Pulmonary artery diastolic and mean diastolic PAP can be calculated from the end-diastolic and early pulmonary regurgitant velocities. PADP = 4 × (end-diastolic pulmonary regurgitant velocity)^2 + RA pressure. The mean PAP can also be estimated as 4 × (early PR velocity)^2 + estimated RA pressure. Once systolic and diastolic pressures are known, mean pressure may also be estimated by the standard formula, mean PAP = 1/3(SPAP) + 2/3(PADP).

Other method to know the mean PAP is from pulmonary acceleration time (AT). Mean PAP = 79 – (0.45 × AT), if in patients with AT less than 120 ms, then formula for mean PAP is 90 – (0.62 × AT) (Figs. 65.5A to D). PVR can be estimated using a simple ratio of peak TR velocity (in meters per second) to the RVOT velocity-time integral (in centimeters) (Fig. 65.6). The Doppler tissue velocities and

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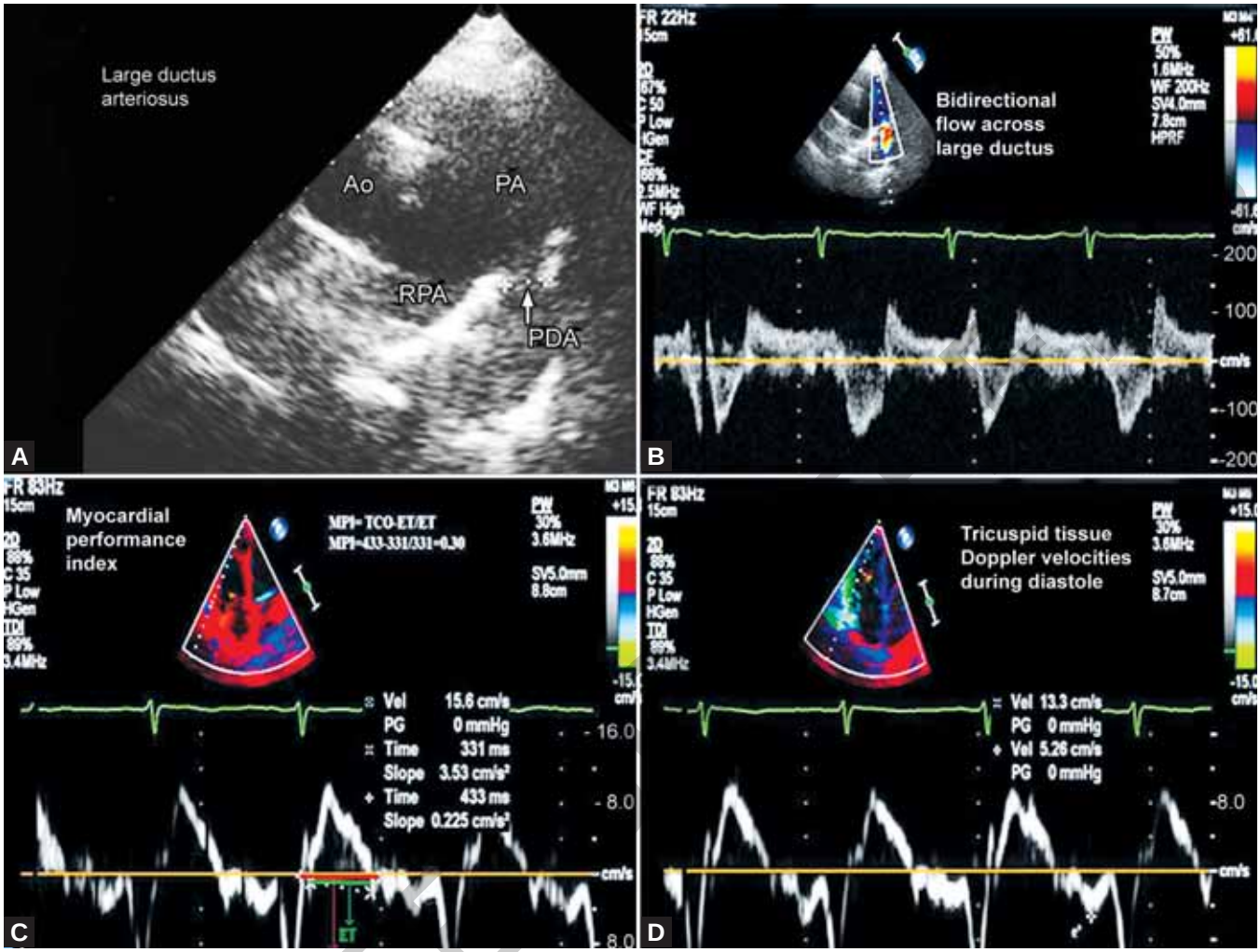

Figs. 65.4A to D: Echocardiographic recording of an Eisenmenger large patent ductus arteriosus (PDA). (A) Short axis view showing large PDA; (B) Demonstrating bidirectional color and Doppler flow; (C) Low radionuclide myocardial perfusion imaging due to right ventricular dysfunction; (D) Tricuspid lateral annular tissue Doppler velocities demonstrating diastolic right ventricular dysfunction.

time intervals obtained at the lateral tricuspid valve annulus are: peak velocity during atrial contraction (Aa), AT, peak velocity during early diastole (Ea), ejection time (ET), myocardial acceleration during isovolumic contraction (IVA) peak myocardial velocity during isovolumic contraction (IVV), and peak velocity during ejection period of systole (Sa). Regional RV strain and strain rate can be measured as research tools.

Even though many echocardiographic parameters can be assessed and estimated, Doppler studies are too unreliable for following serial measurements to monitor therapy. Even tricuspid regurgitation (TR) jet velocity in estimation of PASP is not very accurate, whenever there is doubt better to do catheterization (CATH) to know the severity of PAH.

Radionuclide Ventriculography

Radionuclide ventriculography can provide useful information regarding RV function. Although PAP cannot be estimated with this technique, there is an inverse relationship between PAP and RV ejection fraction.

Pulmonary Function Tests

Although pulmonary function in patients with PAH is often completely normal, reductions in lung volumes of 20% are common. Elevated PAP causes restrictive physiology. Mainly to diagnose and to detect the severity of obstructive and restrictive lung diseases, pulmonary function tests are performed along with diffusing lung capacity for carbon dioxide (DLCO). Arterial blood gas (ABG) analysis will

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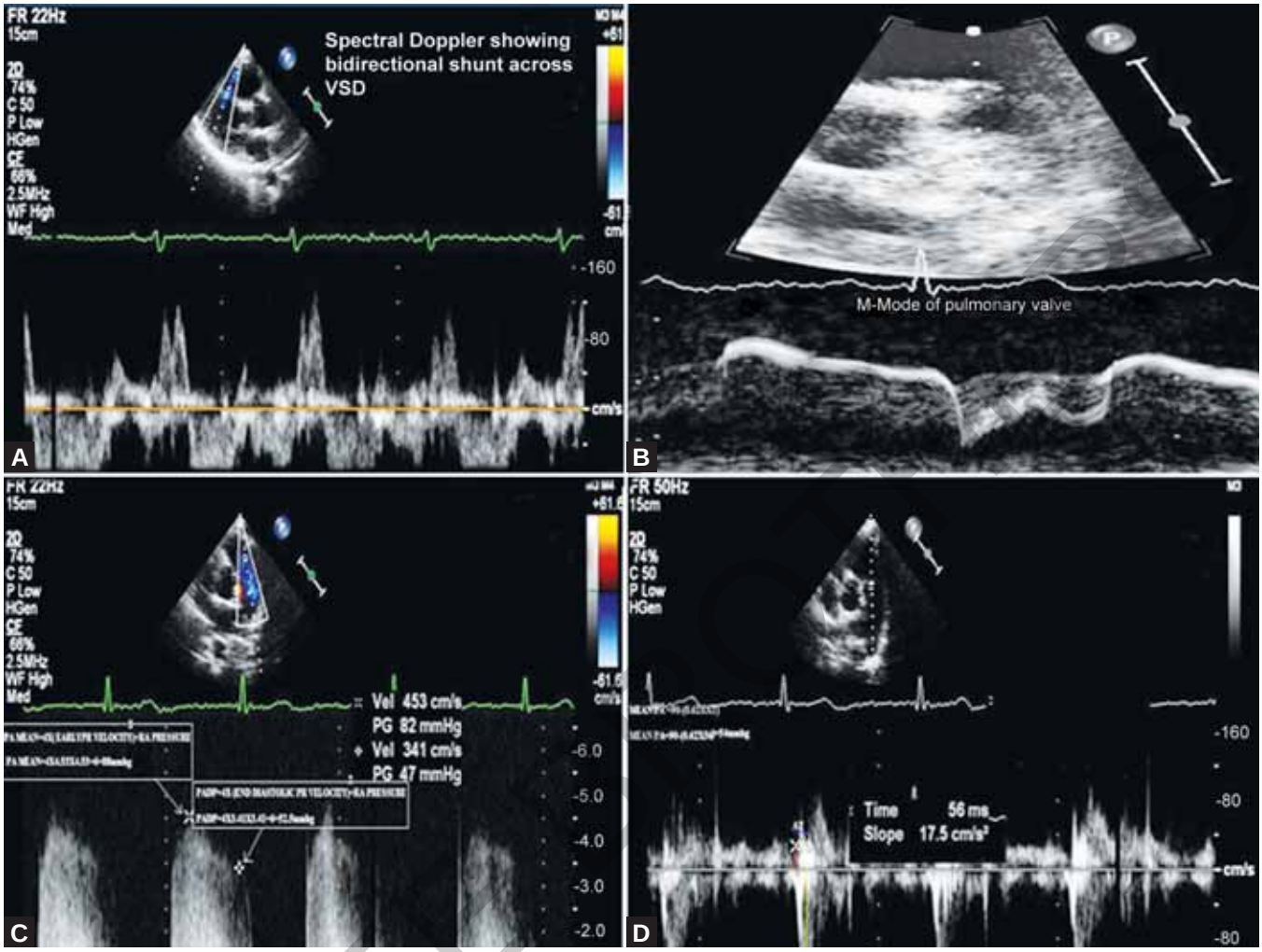

Figs. 65.5A to D: Echocardiographic recording of a large muscular ventricular septal defect (VSD) with severe PAH. (A) Muscular VSD with bidirectional shunt; (B) M-mode of pulmonary valvulogram in PAH; (C) Pulmonary artery mean and diastolic pressure estimation with pulmonary regurgitant velocity; (D) Estimation of mean pulmonary artery pressure from acceleration time of pulmonary jet velocity.

show the hypoxia, hypercarbia and in a sick patient with RV failure, the severity of the acidosis can also be detected.

Lung Scintigraphy

Patients with PAH may reveal a relatively normal perfusion pattern or diffuse, patchy perfusion abnormalities. A perfusion lung scan will reliably distinguish patients with PAH from those who have PH secondary to chronic pulmonary thromboembolism.

Computed Tomography

Spiral chest computed tomography (CT) scans have been used successfully in diagnosing chronic thromboembolic PH. In addition to visualization of thrombi in the pulmonary vasculature with contrast enhancement (Figs. 65.7A to F), a mosaic pattern of variable attenuation compatible with irregular pulmonary perfusion can be determined on the nonenhanced CT scan. Marked variation in the size of segmental vessels is also a specific feature of chronic thromboembolic disease. High-resolution CT is the best test by which to diagnose interstitial lung disease and emphysema.

Exercise Testing

Routine treadmill test with Naughton protocol in less symptomatic patient and 6-minute walk test in more severely symptomatic patient are used to assess the

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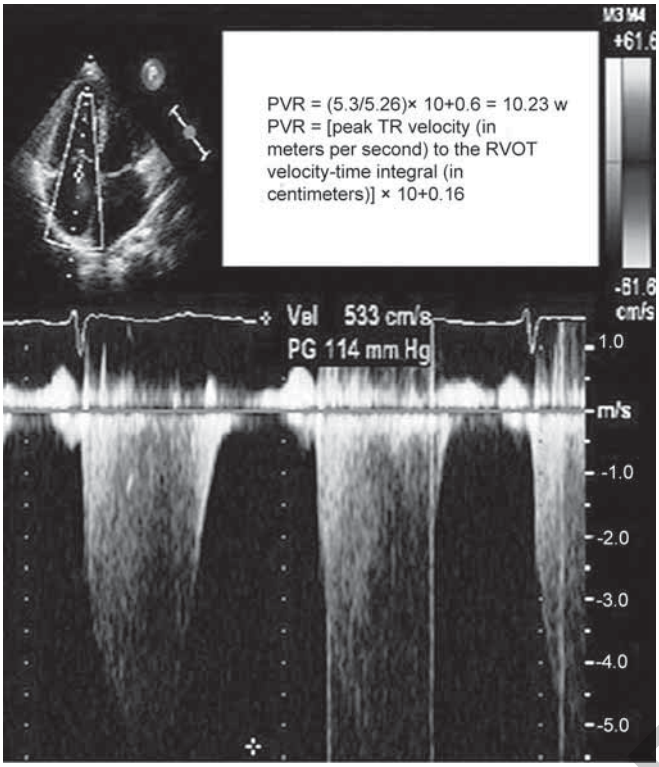

Fig. 65.6: Echocardiographic recording of the same patient described in Figure 65.4, showing high pulmonary vascular resistance (PVR).

efficacy of therapy. Severe exercise-induced hypoxemia should cause consideration of a right-to-left shunt. Dyspnea during exercise in PH is attributable to worsening ventilation-perfusion mismatch, lactic acidosis, and arterial hypoxemia.

Cardiac Catheterization

Cardiac catheterization also establishes the severity of the disease and allows an assessment of prognosis. By definition, patients with PAH should have a low or normal pulmonary capillary wedge pressure (PCWP). It has been shown that left ventricular diastolic compliance becomes impaired in patients with PAH and parallels the severity of the disease; thus, pulmonary capillary wedge pressure tends to rise slightly in the late stages of PAH, although it rarely exceeds 16 mm Hg. It can be extremely difficult to pass a catheter into the pulmonary artery in patients with PH, because of the tricuspid regurgitation and pulmonary regurgitation. A specific flow-directed thermodilution balloon catheter has been developed for patients with PH (American Edwards Laboratories, Irvine, CA); it has an extra port for the placement of a 0.28-inch guidewire to provide better stiffness to the catheter.

Response to Pulmonary Vasodilator Therapy

Many pulmonary vasodilators are studied to detect the responders of chronic vasodilator therapy.[27] Adenosine is an intermediate product in the metabolism of adenosine triphosphate that has potent vasodilator properties through its action on specific vascular receptors. It is believed to stimulate the endothelial cell and vascular smooth muscle receptors of the A_2 type, which induce vascular smooth muscle relaxation by increasing cyclic adenosine monophosphate. In patients with PAH, adenosine has been shown to be a potent vasodilator and predictive of the chronic effects of intravenous prostacyclin as well as the calcium channel blockers (CCBs). Adenosine has an extremely short half-life (<1–6 seconds), which provides safety due to its rapid dissolution, should any adverse side effects occur. It is administered intravenously as an infusion in doses of 50 μg/kg/min and titrated upward every 2 minutes until the patient develops chest tightness or dyspnea.

Epoprostenol has been used in vasoreactivity studies in patients with PAH. Like adenosine, its short half-life allows use of the drug to be discontinued if any acute adverse effects result. Also similar to adenosine, it is administered incrementally, at 2 ng/kg/min and increased every 15–30 minutes until systemic effects such as headache, flushing, or nausea occur, which limits the acute dose titration. Favorable acute effects from epoprostenol are predictive of a favorable response to CCBs.

Adenosine and epoprostenol possess potent inotropic properties, in addition to their ability to vasodilate the pulmonary vascular bed. When using these drugs for the acute testing of patients, one needs to pay particular attention to changes in cardiac output that occur in association with the changes in PAP. An increase in cardiac output with no change in PAP will result in a reduction in calculated PVR and may be erroneously interpreted as a vasodilator response.

Nitric oxide is also a useful drug to test pulmonary vasoreactivity. It binds very rapidly to hemoglobin with high affinity and is thereby inactivated. Inhalation of NO gas results in selective pulmonary vascular effects without influencing the systemic circulation. It can also predict the effectiveness

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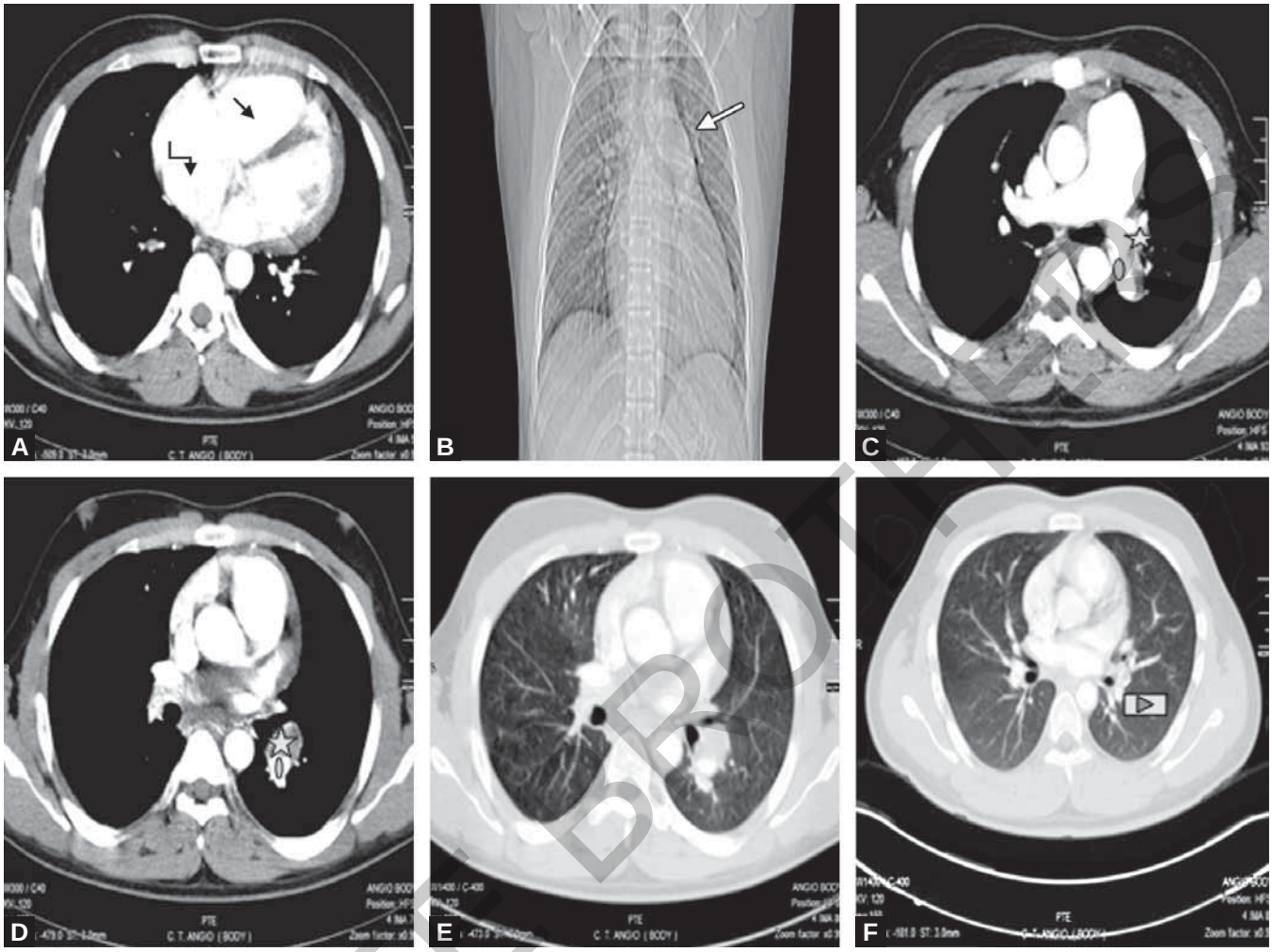

Figs. 65.7A to F: Plain and contrast computed tomography scans of a 12-year-old boy of nephritic syndrome presented with subacute pulmonary thromboembolism. (A) Dilated RV (↓) and RA; (B) Arrow showing prominent pulmonary artery; (C) Showing eccentric thrombus (✶) in left pulmonary artery; (D) Mediastinal window showing thrombus and normal lumen in left descending pulmonary artery; (E) Same scan in lung window; (F) Showing pulmonary oligemia (►) of left lower lobe.

of CCBs. Nitric oxide (NO) differs importantly from adenosine and epoprostenol in that it has little effect on cardiac output. It is usually given via facemask at 20–40 ppm.

It must be emphasized that hemodynamic assessment of the entire circulatory system is essential when determining the influence of drugs in these patients. Small changes in PAP are usually caused by variability rather than direct drug influence. Changes in PVR cannot be directly measured, but are computed by the change in PAP and cardiac output simultaneously. The commonly used thermodilution cardiac output method can be associated with large errors in reproducibility; hence, particular care should be taken in the methodology of thermodilution used in these patients. In addition, when an underlying right-to-left shunt exists, the Fick's determination of cardiac output is required.

Changes in PCWP can have important influences on the determination of PVR. A rising capillary wedge pressure secondary to increased cardiac output may be the first sign of impending left ventricular failure and an adverse effect of a drug, whereas the calculated PVR may become lower and suggest a beneficial effect. RA pressure also reflects the filling characteristics of the RV. An RA pressure increase in the face of rising cardiac output suggests RV diastolic

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dysfunction. Effective vasodilator drugs can result in vasodilation of blood vessels supplying poorly ventilated areas of the lung and can worsen hypoxemia.

Pulmonary Angiography

Although pulmonary angiography carries an increased risk in patients with PH, it can be performed safely if adequate precautions are taken. Maintenance of adequate oxygenation by the administration of supplemental oxygen and the avoidance of vasovagal reactions and rapid treatment of those that occur with intravenous atropine should reduce the associated risk in this patient group. Continuous arterial pressure monitoring is advised and nonionic contrast agents appear to be better tolerated.

Pulmonary Wedge Angiogram

Abnormal structural changes in pulmonary vascular bed represented in wedge angiogram (Fig. 65.8) are:[28]

- Sparsity of arborization of the pulmonary tree
- Abrupt termination of arteries—the rate of tapering of the arteries is assessed by measuring the length of a segment over which the lumen diameter narrows between 2.5 and 1.5 mm.
- Tortuosity and narrowing of small arteries
- Reduced background capillary filling.

Pitfalls and limitations in the interpretation of the pulmonary wedge angiogram:

- Pulmonary stenosis or previous placement of pulmonary artery band gives the impression of rapid tapering.

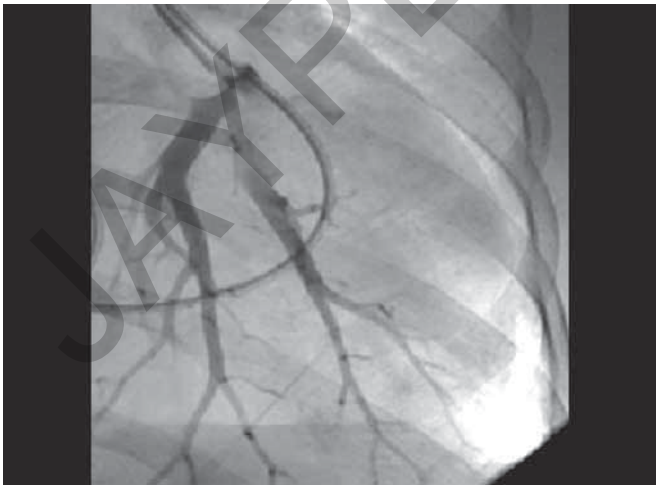

Fig. 65.8: Pulmonary wedge angiogram in a young female with idiopathic pulmonary arterial hypertension.

- With very advanced vascular disease, there is sometimes such extensive intimal hyperplasia that the vessel appears narrowed all the way from hilum, so that abrupt tapering is no longer apparent. In this, however, background haze is absent and the pulmonary circulation time is usually prolonged.
- If the injection of contrast fails to fill the vessels all the way out to the pleura, the background will appear dark.
- If the balloon does not completely occlude the vessel, the false impression of a dense background will be created owing to the filling of capillaries and veins.

Lung Biopsy

Even after catheterization if there is controversy regarding operability, then lung biopsy may be indicated in this subgroup of patients. Grading of severity of abnormality in growth and development of pulmonary vascular bed is:[29-31]

- Grade A—*Mechanism*: Precocious differentiation to mature smooth muscle cells (the pericyte in nonmuscular region of the artery and the intermediate cell in the partially muscular region)—probably stretch is the stimulus for smooth muscle cell differentiation from precursor cells.
  - Abnormal extension of muscle into small peripheral arteries
  - Mild increase in wall thickness of muscular arteries (<1.5 times normal).
  - Hemodynamic correlation—increased pulmonary blood flow, increased pulse pressure, normal mean PAP
- Grade B—*Mechanism*: Hypertrophy as well as hyperplasia of preexisting smooth muscle cells and also increase in the intercellular connective tissue proteins
  - Mild Grade B
    - More severe medial hypertrophy of normal muscular arteries
    - Medial thickness more than 1.5 to less than 2 times normal.
    - Hemodynamic correlation—PH is usually present.
  - Severe Grade B
    - Medial wall thickness more than 2 times normal
    - Hemodynamic correlation—pulmonary pressure value more than half of the systemic level
- Grade C—*Mechanism*: Failure of new vessels to grow normally, although some loss of arteries may also occur.
  - Mild Grade C
    - Arterial concentration is reduced

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- Arterial size is reduced
- Hemodynamic correlation – PVR > 3.5U/m^2

– Severe Grade C
- Artery number is less than half of normal
- Hemodynamic correlation—PVR more than 6 U/m^2.

Quantitative techniques have been applied to the analysis of lung biopsy tissue prepared by frozen section to decide between a palliative or corrective procedure when preoperative hemodynamic data are borderline or difficult to interpret more in Fontan procedure.

TYPES OF PULMONARY HYPERTENSION

Idiopathic Pulmonary Hypertension

Pathological Features

It has been proposed that somatic mutation rather than nonselective cell proliferation occurring in response to injury accounts for the growth advantage of endothelial cells in patients with Idiopathic pulmonary artery hypertension (IPAH). Heterogeneity in the smooth muscle and fibroblast populations also contributes to discordance between phenotype and function. Interconversion between cell types (fibroblast to smooth muscle cell or endothelium to smooth muscle cell) in addition to neovascularization may occur. As already mentioned, in pathophysiology of PAH, classically hypertensive and thromboembolic pulmonary arteriopathy changes are seen.

The clinical features and investigations in IPAH are as those mentioned for PAH. The most extensive study on the natural history of IPAH was reported from the National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension from 1981 to 1987. The study included the long-term follow-up of 194 patients in whom IPAH was diagnosed by established clinical and hemodynamic criteria. Sixty-three percent of the patients were female and the mean age was 36 ± 15 years (range 1–81 years) at the time of diagnosis. The mean interval from the onset of symptoms to diagnosis was 2 years, and the most common initial symptoms were dyspnea (80%), fatigue (19%), syncope or near-syncope (13%), and Raynaud phenomenon (10%). No ethnic differentiation was observed, with 12.3% of patients being black and 2.3% being Hispanic.

Univariate analysis from the NIH Registry has pointed to the mean RA pressure, mean PAP, and cardiac index, as well as the DLCO, as being significantly related to mortality. The NYHA functional classification was also strongly related to survival. A reduced left ventricular ejection fraction in PAH is related to interventricular dependence or extrinsic compression of the left main coronary artery by the pulmonary artery.

Clinical Course

With the onset of overt RV failure manifested by worsening symptoms and systemic venous congestion, patient survival is generally limited to approximately 6 months. The most common cause of death in patients with IPAH in the NIH Registry was progressive right-sided heart failure (47%). Sudden cardiac death was limited to patients who were in NYHA functional Class IV. The remainder of the patients died of other medical complications, such as pneumonia or bleeding, which suggests that patients with IPAH do not tolerate coexistent medical conditions well.

Familial Pulmonary Arterial Hypertension

The prevalence of familial PAH (FPAH) is uncertain, but it occurs in at least 6% of cases and the incidence is likely higher.[32] The age of onset is variable and the low penetrance of the gene confers only about a 20% likelihood of development of the disease. The observation that fewer males are born in PAH families than in the population at large suggests that the PAH gene might influence fertilization or cause male fetal wastage. Patients with FPAH have a similar female-to-male ratio age of onset and natural history of the disease as those with IPAH. Vertical transmission has been demonstrated in as many as five generations in one family and is indicative of a single autosomal dominant gene for PAH.

Secondary Pulmonary Arterial Hypertension

Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

Increased pulmonary blood flow from hyperthyroidism and beriberi have been reported to be associated with the development of unexplained PH, which suggests that high pulmonary blood flow, rather than being mere coincidence is the basis for the development of PH in patients with pretricuspid shunts, such as atrial septal defect or anomalous pulmonary venous drainage. The clinical features and investigations in PAH associated with congenital heart diseases are as those mentioned for PAH.

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Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases

One-third of CREST (calcinosis, Raynaud syndrome, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome patients, two-thirds of mixed connective disorder patients, and nearly one-fourth of systemic lupus erythematosus patients develop PAH. Pulmonary hypertension has also been described in patients with polymyositis, dermatomyositis, and rheumatoid arthritis. Most of the time PAH is insidious in onset with a slowly progressive course and early recognition becomes difficult. Arterial hypoxemia is characteristic and should also prompt an evaluation of possible PH in these patients. The clinical features and investigations in PAH associated with connective tissue diseases are as those mentioned for PAH. Because hypoxemia is so common, patients should be tested with pulse oximetry during exercise and supplemental oxygen should be used whenever indicated. The prognosis of patients with connective tissue disease in whom PH develops is poor.

Pulmonary Arterial Hypertension Associated with Portal Hypertension

A large postmortem study from the Johns Hopkins Hospital has shown that the prevalence of unexplained or PH in patients with cirrhosis is 5.6 times higher than that of IPAH alone. Although the mechanisms are uncertain, several possibilities are consistent. Portal hypertension itself induces numerous modifications in the vascular media that may trigger a cascade of intracellular signals and/or cause activation or repression of various genes in endothelial and smooth muscle cells. Increased levels of several vasoactive mediators, cytokines, and growth factors have been demonstrated in patients with portal hypertension, including serotonin and interleukin-1. Other angiogenic factors such as hepatocyte growth factor or vascular endothelial growth factor may be involved in pulmonary artery remodeling. Severe PH is considered a contraindication to liver transplantation because of the risk of irreversible right-sided heart failure.

Pulmonary Arterial Hypertension Associated with Human Immunodeficiency Virus Infection

A large case-control study of HIV-associated PAH conducted in the Swiss HIV Cohort study reported the cumulative incidence to be 0.6% in the entire HIV-infected population. PAH was diagnosed in patients in all stages of HIV infection and without an obvious relationship to immune deficiency, because it was unrelated to the CD4 cell counts. Possible mechanism of production of PAH is unknown and may be mediated by release of inflammatory mediators or by autoimmune mechanisms.

Pulmonary Arterial Hypertension Related to Anorexigens

Fenfluramine and aminorex can produce PH.[33] These drugs can cause pulmonary vasoconstriction by inhibiting voltage-gated potassium channels in the smooth muscle cells of the resistance level pulmonary arteries. Although the degree of pulmonary vasoconstriction noted was small, it increased dramatically when NO synthase was inhibited.

Pulmonary Hypertension Related to Sickle Cell Disease

Cardiopulmonary complications are common in sickle cell disease. The cause of PH, which has been reported in 20–32% of sickle cell disease patients is multifactorial with contributing factors including hemolysis, impaired NO bioavailability, chronic hypoxemia, high cardiac output, thromboembolism, and parenchymal and vascular injury caused by sequestration of sickle erythrocytes, chronic liver disease, and asplenia.[34] In a recent study by Florence Parent in adults with sickle cell disease, the prevalence of PH as confirmed on right heart catheterization was 6%. Echocardiographic evaluation alone had a low positive predictive value for PH.[35]

Persistent Pulmonary Hypertension of the Newborn

Although persistent PH of the newborn can vary in severity, severe cases are usually life-threatening. Mechanism of development of PAH in newborn is mentioned in Flowchart 65.9. It is usually associated with severe hypoxemia and the need for mechanical ventilation. Echocardiographic findings of severe PH and right-to-left shunting at the level of the ductus arteriosus or foramen ovale are common. Inhaled NO, intravenous epoprostenol, and extracorporeal membrane oxygenation have also been used.

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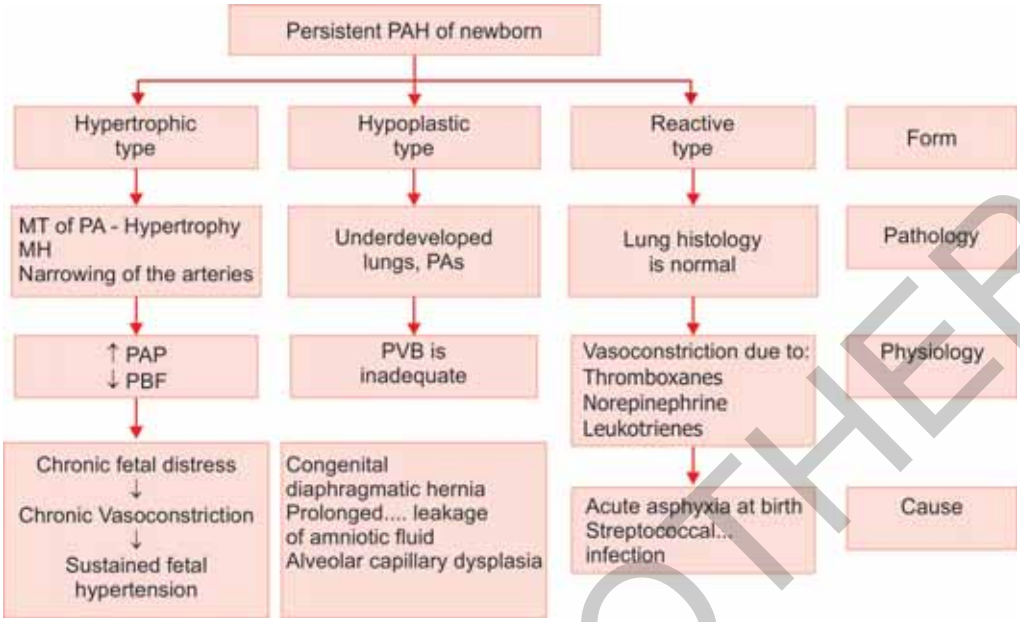
Flowchart 65.9: Diagrammatic representation of types, causes, and pathophysiology of persistent pulmonary hypertension.



(MH, medial hypertrophy; MT, muscular tissue; PA, pulmonary arteries; PAP, pulmonary arterial pressure; PBF, pulmonary blood flow; PVB, pulmonary vascular bed).

Pulmonary Veno-occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare form of PAH (Table 65.2).[36]

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis is a very rare cause of PH.[37] Histological findings often are also common. Most patients appear to be young adults. It is difficult to distinguish pulmonary capillary hemangiomatosis from IPAH clinically.

The clinical course of patients with this condition is usually one of progressive deteriorations leading to severe PH, right-sided heart failure, and death (Table 65.3).

Pulmonary Venous Hypertension

Considerable variability in pulmonary arterial vasoconstriction occurs in response to pulmonary venous hypertension. Marked reactive PH with SPAP in excess of 80 mm Hg occurs in less than one-third of patients whose pulmonary venous pressures are elevated more than 25 mm Hg. Chronic elevation of pulmonary venous pressures as a result of other disorders, such as left ventricular diastolic dysfunction, also results in a disproportionate elevation in PAP in a subset of patients.

The mechanisms involved in elevating PVR are unclear. In addition to hypertrophy of the media of the vasculature, a neural component may be present. An elevation in

Table 65.2: Diagnosis, pathology, and management of pulmonary veno-occlusive disease.

Features	*Information*
Histopathological diagnosis	Presence of obstructive eccentric fibrous intimal pads in the pulmonary veins and venules. Arterialization of the pulmonary veins, medial hypertrophy and muscularization of the arterioles with eccentric intimal fibrosis
Pulmonary capillary wedge pressure	Normal, ↑in late stages
Chest radiograph	Increase in basilar bronchovascular markings
Perfusion lung scan	Diffuse, patchy nonsegmental abnormalities
Chest computed tomographic scan	Smooth interlobular septal thickening, ground-glass opacities, and a mosaic attention pattern
Treatment	Unsatisfactory. Any therapy needs close supervision and early referral of the patient for lung transplantation should be considered.

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She is a Fellow of the American College of Cardiology and has presented numerous lectures, panel discussions, and posters at several national and international scientific conferences. She has written many book chapters and contributed to eight medical textbooks. She is a reviewer for multiple journals including Journal of the American College of Cardiology, Journal of the American Society of Echocardiography, Echocardiography, The Permanente Journal, and International Journal of Cardiology. She actively volunteers for the Hippocrates Circle, Medical Explorers Program and many non-medical organizations.

She has received many awards for her services including Everyday Heroes Awards (2017), The Unsung Hero Award (July 2009), Leon M Cohen Physician Recognition Award (December 2005), American Heart Association/Wyeth-Ayerst Women in Cardiology Award (1998), and the Harrison Fellowship Award (1996).

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