The complexities of lymphatic cannulation and the risk of lymphangitis associated with the contrast agent limit the utility of lymphangiography. A novel technique of optical imaging with a near-infrared fluorescence dye may enable quantitative imaging of lymph flow.

TREATMENT LYMPHEDEMA

Patients with lymphedema of the lower extremities must be instructed to take meticulous care of their feet to prevent recurrent lymphangitis. Skin hygiene is important, and emollients can be used to prevent drying. Prophylactic antibiotics are often helpful, and fungal infection should be treated aggressively. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss.

Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Diuretics are contraindicated and may cause depletion of intravascular volume and metabolic abnormalities.

Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

Therapeutic lymphangiogenesis has been studied in rodent models of lymphedema, but not as yet in humans. Overexpression of vascular endothelial growth factor (VEGF) C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema, and administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of postsurgical lymphedema. Clinical trials in patients with lymphedema are required to determine efficacy of gene transfer (cell-based) therapies for lymphedema.

304 Pulmonary Hypertension

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Pulmonary hypertension (PH) is a spectrum of diseases involving the pulmonary vasculature, and is defined as an elevation in pulmonary arterial pressures (mean pulmonary artery pressure >22 mmHg). Pulmonary arterial hypertension (PAH) is a relatively rare form of PH and is characterized by symptoms of dyspnea, chest pain, and syncope. If left untreated, the disease carries a high mortality rate, with the most common cause of death being decompensated right heart failure. There have been significant advances in this field in regard to understanding the pathogenesis, diagnosis, and classification of PAH. Despite these significant advances, there is still a substantial delay in diagnosis of up to 2 years. In many cases, patients whose primary complaint is dyspnea on exertion are frequently misdiagnosed with more common diseases such as asthma or chronic obstructive pulmonary disease. The availability of newer drugs has resulted in a radical change in the management of this disease with significant improvement in both quality of life and mortality. A delay in diagnosis results in an obvious delay in the initiation of appropriate treatment. Clinicians should be able to recognize the signs and symptoms of PH and to complete a systematic workup in patients suspected of having it. In this way, early diagnosis, prompt treatment, and improved outcomes for patients become achievable.

PATHOBIOLOGY

Vasoconstriction, vascular proliferation, thrombosis, and inflammation appear to underlie the development of PAH (Fig. 304-1). In long-standing PH, intimal proliferation and fibrosis, medial hypertrophy, and in situ thrombosis characterize the pathologic findings in the pulmonary vasculature. Vascular remodeling at earlier stages may be confined to the small pulmonary arteries. As the disease advances, intimal proliferation and pathologic remodeling progress, resulting in decreased compliance and increased elastance of the pulmonary vasculature. The outcome is a progressive increase in the right ventricular afterload or total pulmonary vascular resistance (PVR) and, thus, right ventricular work. In subjects with moderate to severe pulmonary vascular disease with significantly increased PVR, as the resting PVR increases, there will be a corresponding increase in mean pulmonary artery pressure (PAP) until the cardiac output (CO) is compromised and starts to fall. With a decline in CO, the PAP will fall. As CO declines as a result of increased afterload and decreased contractility, tachycardia is a compensatory response. Tachycardia decreases filling time and, thus, preload, and results in a reduced fraction of stroke volume available to distend the pulmonary vascular tree.

Abnormalities in multiple molecular pathways and genes that regulate the pulmonary vascular endothelial and smooth muscle cells have been identified (Table 304-1). These abnormalities include decreased expression of the voltage-regulated potassium channel, mutations in the bone morphogenetic protein receptor-2, increased tissue factor expression, overactivation of the serotonin transporter, hypoxia-induced activation of hypoxia-inducible factor-1α, and activation of nuclear factor of activated T cells. As a result, there is a decrease in apoptosis of the smooth muscle cells and the emergence of apoptosis-resistant endothelial cells that promote their accumulation and can obliterate the vascular lumen. In addition, thrombin deposition in the pulmonary vasculature from the prothrombotic state that develops as an independent abnormality or as a result of endothelial dysfunction may amplify vascular cell proliferation and the obliterative arteriopathy.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of PH can be missed without a reasonable index of suspicion. Dyspnea is the most common presenting symptom, but this complaint is far from specific for the diagnosis of PH. PH symptoms are insidious and overlap considerably with many common conditions, including asthma and other lung disease and cardiac disease. The symptoms of PH are often nonspecific and variable. Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and frank syncope are less common and associated with more advanced disease. On examination, 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 P_2 component of the second heart sound, a right-sided S_3 or S_4, and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are often concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma, and crackles and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.

Once clinical suspicion is raised, a systematic approach to diagnosis and assessment is essential. An echocardiogram with (if indicated) a *bubble study* is the most important screening test. Echocardiography is important for the diagnosis of PH and often essential for determining the cause. All forms of PH may demonstrate a hypertrophied and