pulmonale. Perhaps most important is that a small embolus may presage a larger one. In the presence of an underlying predisposing condition, patients with a pulmonary embolus have a 30% chance of suffering a second embolus.

Prevention of pulmonary embolism is a major clinical challenge for which there is no easy solution. Prophylactic therapy includes early ambulation in postoperative and postpartum patients, elastic stockings and graduated compression stockings for bedridden patients, and anticoagulation in high-risk individuals. Treatment of pulmonary embolism includes anticoagulation and supportive measures; thrombolysis may have some benefit in those with severe complications (e.g., shock), but carries a high risk of bleeding. Those at risk of recurrent pulmonary embolism in whom anticoagulation is contraindicated may be fitted with an inferior vena cava filter (an "umbrella") that catches clots before they reach the lungs.

KEY CONCEPTS

Pulmonary Embolism

- Almost all large pulmonary artery thrombi are embolic in origin, usually arising from the deep veins of the lower leg.
- Risk factors include prolonged bed rest, leg surgery, severe trauma, CHF, use of oral contraceptives (especially those with high estrogen content), disseminated cancer, and genetic diseases of hypercoagulability.
- The vast majority (60% to 80%) of emboli are clinically silent, a minority (5%) cause acute cor pulmonale, shock, or death (typically from large "saddle emboli"), and the remaining cause pulmonary infarction.
- Risk of recurrence is high.

Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest. Based on underlying mechanisms, the World Health Organization has classified pulmonary hypertension into five groups. These groups are: (1) pulmonary arterial hypertension, a diverse collection of disorders that all primarily impact small pulmonary muscular arteries; (2) pulmonary hypertension secondary to left-heart failure; (3) pulmonary hypertension stemming from lung parenchymal disease or hypoxemia; (4) chronic thromboembolic pulmonary hypertension; and (5) pulmonary hypertension of multifactorial basis.

Pathogenesis. As can be gathered from the classification above, pulmonary hypertension has diverse causes. It is most frequently associated with structural cardiopulmonary conditions that increase pulmonary blood flow, pulmonary vascular resistance, or left heart resistance to blood flow. Some of the more common causes are the following:

- *Chronic obstructive or interstitial lung diseases* (group 3). These diseases obliterate alveolar capillaries, increasing pulmonary resistance to blood flow and, secondarily, pulmonary blood pressure.
- *Antecedent congenital or acquired heart disease* (group 2). Mitral stenosis, for example, causes an increase in left atrial pressure and pulmonary venous pressure that is eventually transmitted to the arterial side of the pulmonary vasculature, leading to hypertension.
- *Recurrent thromboemboli* (group 4). Recurrent pulmonary emboli may cause pulmonary hypertension by reducing the functional cross-sectional area of the pulmonary vascular bed, which in turn leads to an increase in pulmonary vascular resistance.
- *Autoimmune diseases* (group 1). Several of these diseases (most notably systemic sclerosis) involve the pulmonary vasculature and/or the interstitium, leading to increased vascular resistance and pulmonary hypertension.
- *Obstructive sleep apnea* (also group 3) is a common disorder that is associated with obesity and hypoxemia. It is now recognized to be a significant contributor to the development of pulmonary hypertension and cor pulmonale.

Uncommonly, pulmonary hypertension is encountered in patients in whom all known causes are excluded; this is referred to as *idiopathic pulmonary arterial hypertension*. However, this is a bit of a misnomer, as up to 80% of "idiopathic" pulmonary hypertension (sometimes referred to as primary pulmonary hypertension) has a genetic basis, sometimes being inherited in familes as an autosomal dominant trait. Within these families, there is incomplete penetrance, and only 10% to 20% of the family members actually develop overt disease.

As is often the case, much has been learned about the pathogenesis of pulmonary hypertension by investigating the molecular basis of the uncommon familial form of the disease. The first mutation to be discovered in familial pulmonary arterial hypertension was in the bone morphogenetic protein receptor type 2 (BMPR2). Inactivating germline mutations in the BMPR2 gene are found in 75% of the familial cases of pulmonary hypertension, and 25% of sporadic cases. Subsequently other mutations have been discovered that also converge on the BMPR2 pathway and affect intracellular signaling. It has also been demonstrated that BMPR2 is down-regulated in lungs from some idiopathic pulmonary arterial hypertension patients without mutation in its gene.

BMPR2 is a cell surface protein belonging to the TGF-β receptor superfamily, which binds a variety of cytokines, including TGF-β, bone morphogenetic protein (BMP), activin, and inhibin. Although originally described in the context of bone growth, BMP-BMPR2 signaling is now known to be important for embryogenesis, apoptosis, and cell proliferation and differentiation. Details remain to be worked out, but it appears that haploinsufficiency for BMPR2 leads to dysfunction and proliferation of endothelial cells and vascular smooth muscle cells. Because only 10% to 20% of individuals with *BMPR2* mutations develop disease, it is likely that modifier genes and/or environmental triggers also contribute to the pathogenesis of the disorder. A two-hit model has been proposed whereby a genetically susceptible individual with a *BMPR2* mutation requires additional genetic or environmental insults to develop the disease (Fig. 15-29).