volume is readily apparent on the expiratory limb of a flow-volume curve. In the early stages of COPD, the abnormality in airflow is only evident at lung volumes at or below the functional residual capacity (closer to residual volume), appearing as a scooped-out lower part of the descending limb of the flow-volume curve. In more advanced disease, the entire curve has decreased expiratory flow compared to normal.

HYPERINFLATION

Lung volumes are also routinely assessed in pulmonary function testing. In COPD there is often "air trapping" (increased residual volume and increased ratio of residual volume to total lung capacity) and progressive hyperinflation (increased total lung capacity) late in the disease. Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow, because as lung volume increases, elastic recoil pressure increases, and airways enlarge so that airway resistance decreases.

Despite compensating for airway obstruction, hyperinflation can push the diaphragm into a flattened position with a number of adverse effects. First, by decreasing the zone of apposition between the diaphragm and the abdominal wall, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration. Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, they are less capable of generating inspiratory pressures than normal. Third, the flattened diaphragm (with increased radius of curvature, r) must generate greater tension (t) to develop the transpulmonary pressure (p) required to produce tidal breathing. This follows from Laplace's law, $p = 2t/r$. Also, because the thoracic cage is distended beyond its normal resting volume, during tidal breathing the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume.

GAS EXCHANGE

Although there is considerable variability in the relationships between the FEV_1 and other physiologic abnormalities in COPD, certain generalizations may be made. The partial pressure of oxygen in arterial blood Pao_2 usually remains near normal until the FEV_1 is decreased to ~50% of predicted, and even much lower FEV_1 values can be associated with a normal Pao_2, at least at rest. An elevation of arterial level of carbon dioxide ($Paco_2$) is not expected until the FEV_1 is <25% of predicted and even then may not occur. Pulmonary hypertension severe enough to cause cor pulmonale and right ventricular failure due to COPD typically occurs in individuals who have marked decreases in FEV_1 (<25% of predicted) and chronic hypoxemia (Pao_2 <55 mmHg); however, recent evidence suggests that some patients will develop significant pulmonary hypertension independent of COPD severity (Chap. 304).

Nonuniform ventilation and ventilation-perfusion mismatching are characteristic of COPD, reflecting the heterogeneous nature of the disease process within the airways and lung parenchyma. Physiologic studies are consistent with multiple parenchymal compartments having different rates of ventilation due to regional differences in compliance and airway resistance. Ventilation-perfusion mismatching accounts for essentially all of the reduction in Pao_2 that occurs in COPD; shunting is minimal. This finding explains the effectiveness of modest elevations of inspired oxygen in treating hypoxemia due to COPD and therefore the need to consider problems other than COPD when hypoxemia is difficult to correct with modest levels of supplemental oxygen.

RISK FACTORS

CIGARETTE SMOKING

By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Subsequent longitudinal studies have shown accelerated decline in FEV_1 in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking). This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts for the higher prevalence rates of COPD with increasing age. The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males; however, the prevalence of COPD among females is increasing as the gender gap in smoking rates has diminished in the past 50 years.

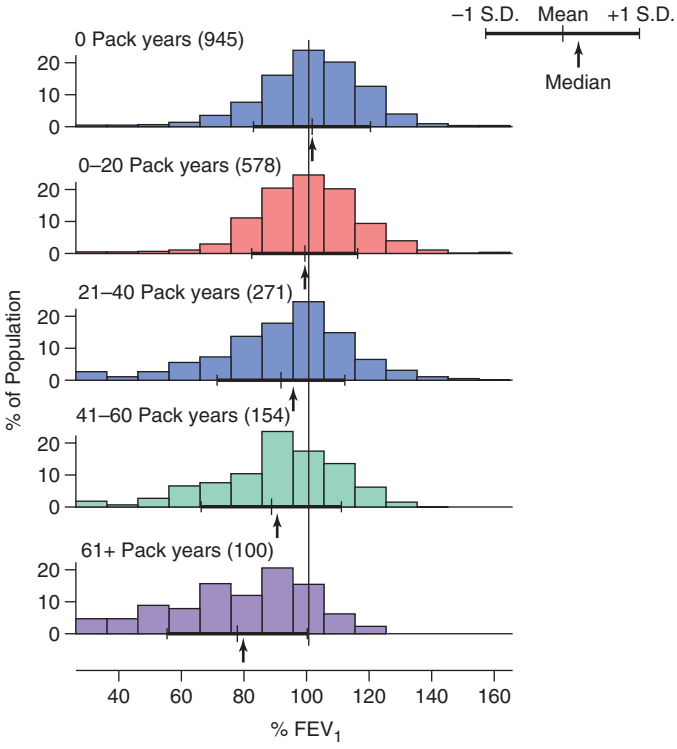

FIGURE 314-2 Distributions of forced expiratory volume in 1 s (FEV_1) values in a general population sample, stratified by pack-years of smoking. Means, medians, and ±1 standard deviation of percent predicted FEV_1 are shown for each smoking group. Although a dose-response relationship between smoking intensity and FEV_1 was found, marked variability in pulmonary function was observed among subjects with similar smoking histories. *(From B Burrows et al: Am Rev Respir Dis 115:95, 1977; with permission.)*

Although the causal relationship between cigarette smoking and the development of COPD has been absolutely proved, there is considerable variability in the response to smoking. Although pack-years of cigarette smoking is the most highly significant predictor of FEV_1 (Fig. 314-2), only 15% of the variability in FEV_1 is explained by pack-years. This finding suggests that additional environmental and/or genetic factors contribute to the impact of smoking on the development of airflow obstruction.

Although cigar and pipe smoking may also be associated with the development of COPD, the evidence supporting such associations is less compelling, likely related to the lower dose of inhaled tobacco by-products during cigar and pipe smoking.

AIRWAY RESPONSIVENESS AND COPD

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine, is one of the defining features of asthma (Chap. 309). However, many patients with COPD also share this feature of airway hyperresponsiveness. The considerable overlap between persons with asthma and those with COPD in airway responsiveness, airflow obstruction, and pulmonary symptoms led to the formulation of the Dutch hypothesis. This suggests that asthma, chronic bronchitis, and emphysema are variations of the same basic disease, which is modulated by environmental and genetic factors to produce these pathologically distinct entities. The alternative British hypothesis contends that asthma and COPD