altitude or in high-performance athletes exerting maximal effort) is oxygen uptake from normal lungs diffusion limited. Diffusion limitation can also occur in interstitial lung disease if substantially thickened alveolar walls remain perfused.

Ventilation/Perfusion Heterogeneity As noted above, for gas exchange to be most efficient, ventilation to each individual alveolus (among the millions of alveoli) should match perfusion to its accompanying capillaries. Because of the differential effects of gravity on lung mechanics and blood flow throughout the lung and because of differences in airway and vascular architecture among various respiratory paths, there is minor ventilation/perfusion heterogeneity even in the normal lung; however, $\dot{V}/\dot{Q}$ heterogeneity can be particularly marked in disease. Two extreme examples are (1) ventilation of unperfused lung distal to a pulmonary embolus, in which ventilation of the physiologic dead space is "wasted" in the sense that it does not contribute to gas exchange; and (2) perfusion of nonventilated lung (a "shunt"), which allows venous blood to pass through the lung unaltered. When mixed with fully oxygenated blood leaving other well-ventilated lung units, shunted venous blood disproportionately lowers the mixed arterial Pa_{O_2} as a result of the nonlinear oxygen content versus P_{O_2} relationship of hemoglobin (Fig. 306e-5). Furthermore, the resulting arterial hypoxemia is refractory to supplemental inspired oxygen. The reason is that (1) raising the inspired FI_{O_2} has no effect on alveolar gas tensions in nonventilated alveoli and (2) while raising inspired FI_{O_2} does increase PA_{CO_2} in ventilated alveoli, the oxygen content of blood exiting ventilated units increases only slightly, as hemoglobin will already have been nearly fully saturated and the solubility of oxygen in plasma is quite small.

A more common occurrence than the two extreme examples given above is a widening of the distribution of ventilation/perfusion ratios; such $\dot{V}/\dot{Q}$ heterogeneity is a common consequence of lung disease. In this circumstance, perfusion of relatively underventilated alveoli results in the incomplete oxygenation of exiting blood. When mixed with well-oxygenated blood leaving higher $\dot{V}/\dot{Q}$ regions, this partially reoxygenated blood disproportionately lowers arterial Pa_{O_2}, although to a lesser extent than does a similar perfusion fraction of blood leaving regions of pure shunt. In addition, in contrast to shunt regions, inhalation of supplemental oxygen does raise the PA_{O_2}, even in relatively underventilated low $\dot{V}/\dot{Q}$ regions, and so the arterial hypoxemia induced by $\dot{V}/\dot{Q}$ heterogeneity is typically responsive to oxygen therapy (Fig. 306e-5).

In sum, arterial hypoxemia can be caused by substantial reduction of inspired oxygen tension; by severe alveolar hypoventilation; by perfusion of relatively underventilated (low $\dot{V}/\dot{Q}$) or completely unventilated (shunt) lung regions; and, in unusual circumstances, by limitation of gas diffusion.

PATHOPHYSIOLOGY

Although many diseases injure the respiratory system, this system responds to injury in relatively few ways. For this reason, the pattern of

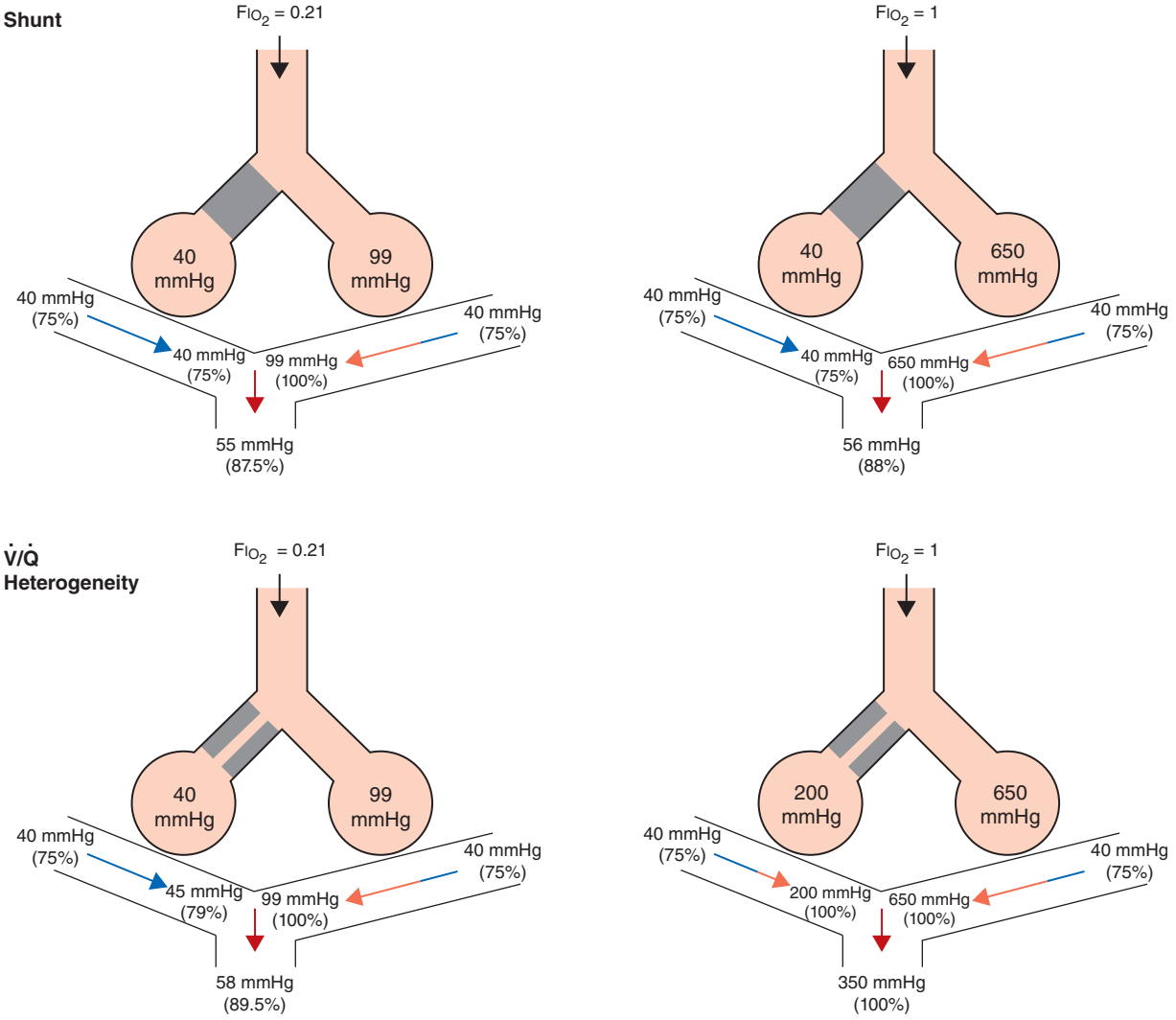

FIGURE 306e-5 Influence of air versus oxygen breathing on mixed arterial oxygenation in shunt and ventilation/perfusion heterogeneity. Partial pressure of oxygen (mmHg) and oxygen saturations are shown for mixed venous blood, for end capillary blood (normal versus affected alveoli), and for mixed arterial blood. FI_{O_2}, fraction of inspired oxygen; $\dot{V}/\dot{Q}$, ventilation/perfusion.