Noncardiogenic Forms of Pulmonary Edema

IT HAS BEEN conventionally taught that accumulation of fluid in the lungs occurs as a result of a primary hydrodynamic imbalance of the normal forces across the alveolar-capillary membrane which results in more fluid being filtered than can be reabsorbed. This process generally is a consequence of left ventricular failure or left atrial hypertension. In the presence of normal left atrial and pulmonary venous pressures, however, lung congestion can stem from a wide variety of other causes. In some instances damage to the alveolar-capillary membrane by toxic agents results in fluid accumulation in the lungs. However in other cases, such as the pulmonary edema associated with heroin overdose, exposure to high altitude, shock caused by peripheral injury, and cerebral trauma, the etiologic mechanisms may be considerably more complex than has previously been suspected. Furthermore, the diagnosis and therapy of such forms of pulmonary edema are still open to question.

Because of the rise in narcotics usage, pulmonary edema associated with heroin overdose has become a medical problem of increasing importance, but its pathogenesis has remained obscure. Pulmonary capillary wedge pressures are normal in patients with lung congestion following heroin overdose. In our own clinical studies 14 of 16 patients with this syndrome were cyanotic, and systemic hypoxia was confirmed by arterial blood gas analysis in all nine subjects in whom such measurements were obtained.1 That hypoxia is an important feature of this syndrome and may play an integral part in its causation was confirmed by Duberstein and Kaufman who noted a marked decrease in systemic arterial oxygen tension in 39 patients with heroin intoxication who subsequently developed pulmonary edema.2 Thus, pulmonary edema due to heroin overdose may be analogous to high-altitude pulmonary edema (see below). Recent work has indicated that the average protein concentration of edema fluid in patients with heroin intoxication was more than double that observed in patients whose lung congestion was due to acute left ventricular failure (5.8 vs 2.7 g %); these data suggest that the permeability of the pulmonary capillaries is greatly increased in patients with heroin-associated pulmonary edema.3 Although central nervous system dysfunction has been proposed as a possible mechanism, the lack of consistent neurologic findings and the normal results of cerebrospinal fluid studies indicate that neurologic dysfunction is an unlikely cause of the pulmonary edema associated with heroin intoxication.2

Unlike patients whose respiratory depression is produced by barbiturates and other sedatives, victims of heroin overdose appear to be singularly prone to develop pulmonary edema. Of 3900 overdose patients admitted to a Copenhagen hospital, only 15 with barbiturate overdose had pulmonary edema, and in 13 it was a late occurrence, secondary to excessive fluid administration.4 Presumably many victims of other types of drug overdose suffer significant hypoxia, but pulmonary edema is nevertheless an unusual complication in overdoses due to other narcotic or sedative drugs. Thus, it is possible that pulmonary edema associated with heroin overdose may result from previously unrecognized actions of heroin or of one of the substances commonly used to adulterate the drug, but no evidence is available to support this speculation.

Systemic hypoxia and elevated pulmonary arterial pressure in the presence of a normal or decreased pulmonary arterial wedge pressure have been consistent findings in the pulmonary edema which occurs at high altitude.

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Hultgren and his co-workers were able to reduce but not eliminate completely the pulmonary hypertension by relief of hypoxia and therefore have hypothesized that pulmonary vasoconstriction resulting from decreased oxygen tension accounts for only a portion of the increased pulmonary vascular resistance found in these patients. Consistent with these data is the observation that in rats exposed to hypoxia the pulmonary arteries developed a perivascular cuff of edema fluid. Histamine has been proposed as an important mediator in the pathogenesis of pulmonary vasoconstriction produced by hypoxia. Under normal circumstances, the bronchial venular system may play a significant role in fluid reabsorption; after administration of histamine, large gaps appear in the endothelium of the bronchial venules, leading to peribronchial interstitial edema, thus indicating that these structures might also be involved in the pathogenesis of pulmonary edema. Since there is some experimental evidence that histamine is released in the lungs in response to hypoxia, this mechanism provides an alternative or additional explanation for the pulmonary edema which occurs with hypoxia. In addition, extraalveolar vessels also may contribute importantly to the formation of interstitial edema. When the pulmonary arterial pressure in excised lungs was raised while alveolar pressure was maintained relatively constant, the arterioles upstream from the capillaries leaked fluid into the alveoli. Intense peripheral venoconstriction in response to hypoxia may cause excessive shunting of blood to the pulmonary circulation; it is possible that this shift of blood to the central circulation contributes to the maintenance of an elevated pulmonary arterial pressure and therefore may also play a role in the causation of high-altitude pulmonary edema in man.

Hypoxia and the local release of vasoactive substances have also been implicated in other forms of noncardiac pulmonary edema. Following a wide variety of insults, including massive peripheral soft-tissue injury, hemorrhagic and endotoxic shock, and pump oxygenator usage, pulmonary damage and lung congestion may occur producing the clinical picture commonly but perhaps inappropriately termed “shock lung.” In addition to the mechanisms outlined previously, injury to the small blood vessels of the lung could also be produced by the arrival of damaged cells, particularly platelets released from the peripheral circulation, and by thrombi and clots dislodged from damaged peripheral regions which are caught in the filter of the pulmonary arterial bed. It is evident that the pathogenesis of pulmonary abnormalities in these cases is not well understood, but the mechanism clearly is complex and may be different among the clinical conditions mentioned above.

In the Conner lecture printed in this issue of Circulation, Fishman observes that the precise role of hypoxemia in causing the fluid-exchanging vessels in the lungs to leak has not been adequately defined. As he indicates, the relative importance of the drainage function of the pulmonary lymphatics, the role of leaks in the bronchial venular system, the place of the reservoir function of the pulmonary interstitial space, and the concept of nonhomogenous distribution of precapillary resistances all require further clarification. Nevertheless, hypoxia as an underlying mechanism, which is at least partially responsible for the pulmonary edema accompanying heroin overdose, ascent to high altitude, and “shock lung,” provides a basis for rational therapeutics. Indeed, oxygen therapy is a mainstay in the treatment of these disorders. Since elevated pulmonary capillary pressures have not been implicated in the pathogenesis of these types of pulmonary edema, it is unlikely that therapy with digitalis is of any benefit. As indicated earlier, local pulmonary release of vasoactive substances, such as histamine, may in part mediate the pulmonary hypertensive response to hypoxia. Thus, hypoxia may serve both to cause pulmonary vasoconstriction and to produce alterations in the permeability of the bronchial venules. It should be pointed out, however, that whether histamine is the mediator of either or both of these responses is a matter of some controversy. Nevertheless,
there is experimental evidence that chlorpheniramine blocks the pulmonary hypertensive response to histamine, and therefore a controlled trial of antihistaminic therapy in these disorders might be worthwhile.

Although there is considerable evidence suggesting that central nervous system lesions may cause acute pulmonary edema, the pathogenesis of this type of lung congestion has remained elusive. Elevation of intracranial pressure in experimental animals produces a sympathetic discharge, causing an increase in total peripheral resistance, which in turn results in a decline in cardiac output, an increase in left atrial pressure, and acute lung congestion. Nevertheless, observations in patients indicating that this mechanism explains pulmonary edema following central nervous system lesions remain scanty. For example, acute pulmonary edema has been found in battle casualties who died virtually instantaneously of head wounds. In patients with elevated intracranial pressure who developed pulmonary edema, symptoms have occurred less than 1 hour following trauma or surgery without significant abnormalities in systemic arterial pressure. After cerebral air embolus during cardiopulmonary bypass, pulmonary edema without left ventricular failure has been observed. Hence, it is unlikely that systemic hypertension and left ventricular failure resulting from an acute sympathetic discharge is an important mechanism underlying acute pulmonary edema following cerebral injury. It has not previously been emphasized that the experimental and clinical observations relative to neurogenic pulmonary edema appear to be widely divergent.

From the foregoing discussion, it is clear that the mechanisms of pulmonary edema underlying heroin overdose, exposure to high altitude, various forms of shock associated with peripheral injury, and cerebral trauma require further elucidation. The ultrastructure of the pulmonary circulation, the mechanisms responsible for transudation and absorption of fluid, the role of the bronchial blood and lymphatic circulation, and the response of these structures to alterations in oxygen tension and humoral agents provide considerable challenge for future research.

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