Mechanisms of Neurogenic Pulmonary Edema

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Introduction

The pulmonary edema that develops quickly after a variety of cerebral insults, such as head injury, epileptic seizures, intracranial hypertension, and subarachnoid hemorrhage, is often accompanied by rapid flooding of airways with a protein-rich edema fluid (Weisman, 1939; MacKay, 1950; Richards, 1963; Simmons et al., 1968; Ciongoli and Posner, 1972; Theodore and Robin, 1976; Fisher and Aboul-Nasr, 1979; Bayne and Simon, 1981; Fein and Rackow, 1982; Lee and Kobrine, 1983). To lay the framework for an understanding of the genesis of neurogenic pulmonary edema, a schematic representation of the pulmonary capillary-tissue-lymphatic system is indicated in Figure 1. Transcapillary fluid filtration is governed by the four Starling forces represented in the equation (Fig. 1): capillary hydrostatic pressure (Pc), plasma colloid osmotic pressure (πp), interstitial hydrostatic pressure (Pi), and interstitial tissue colloid osmotic pressure (πi). The plasma protein concentration is greater than the tissue fluid and lymph protein concentrations (Fig. 1). The lymph flow represents an overflow system. The tight alveolar interepithelial junctions in the normal lung (Taylor, 1981) restrict solute and water movement into the airspaces (Fig. 1). The protein concentration of airway edema fluid in neurogenic pulmonary edema approached that of plasma (Theodore and Robin, 1976; Fein and Rackow, 1982), suggesting that increases in permeability of pulmonary capillaries and alveolar epithelium to proteins are prominently involved in the development of pulmonary edema. Morphological studies in experimental animal models have supported these clinical observations (Hucker et al., 1976; Minnear and Connell, 1981). Since pulmonary arterial hypertension has been observed with the pulmonary edema in experimental animals and patients after central nervous system (CNS) injury (Sarnoff and Sarnoff, 1952; Wray and Nicotra, 1978), a rise in Pc may also be an important factor in edema formation. A purpose of this review is to discuss the relative roles of increases in permeability vs. capillary hydrostatic pressure in the development of neurogenic pulmonary edema.

The rise in intracranial pressure, which is often observed in conjunction with neurogenic pulmonary edema (Ducker and Simmons, 1968; Simmons et al., 1968), may be a requirement for the development of pulmonary edema. Intracranial hypertension elicits the cardiopulmonary responses such as systemic arterial hypertension, left atrial hypertension, and pulmonary vasoconstriction that may be involved in pulmonary edemagenesis. Therefore, in this review, these responses to intracranial hypertension, the mechanisms mediating these responses, and their role in the development of pulmonary edema will be discussed.

Lesions of specific anatomical sites in the brainstem and hypothalamus have been shown to lead to pulmonary edema. The following section reviews the role of CNS structures in the genesis of neurogenic pulmonary edema.

Neuroanatomical Sites Resulting in Pulmonary Edema

Medulla

Brainstem lesions are clinically associated with pulmonary arterial hypertension and pulmonary edema and have been experimentally shown to cause these changes (Rossi and Graf, 1976; Lee and Kobrine, 1983). A high incidence of pulmonary edema was observed in patients with extensive medullary damage around dorsal vagal nuclei and medial reticular nuclei (Rossi and Graf, 1976; Yamour et al., 1980). The detailed studies of Chen et al. (1973, 1976) in rats have delineated the preeminent role of the medulla oblongata in pulmonary edema formation. Systemic arterial hypertension and pulmonary edema occurred after cerebral compression. These responses were not prevented by vagotomy, adrenalectomy, or decerebration, but were abolished by
FIGURE 1. A schematic representation of the pulmonary capillary tissue-lymphatic system. Starling's forces represented in the Starling equation are capillary hydrostatic pressure (Pc), plasma colloid osmotic pressure (Jp), tissue hydrostatic pressure (Pi), and colloid osmotic pressure of tissue fluid (Jt). Jv = JL = net transvascular fluid filtration rate, Kf = capillary filtration coefficient or hydraulic conductivity, and α = protein reflection coefficient. The alveolar epithelial junctions are tight compared to the interendothelial junctions in lung, and thereby restrict solute transport into the airspaces. The dots represent plasma proteins in plasma, tissue fluid, and lymph. The lymph flow represents the overflow in the system, i.e., the difference between the amount of fluid filtered and the amount reabsorbed. A major determinant of Pc is the pre-to-post-capillary resistance ratio as regulated by the smooth muscle tone of the arteries and veins.

The specific site in the medulla responsible for the pulmonary edema after cerebral compression is not clear. Doba and Reis (1972, 1973, 1974) noted that fulminant pulmonary edema developed in rats as a side effect of systemic hypertension after bilateral lesions of the nucleus tractus solitarius (NTS), a medullary termination point of vagus and glossopharyngeal afferents from arterial baroreceptors and chemoreceptors. The effenter fibers from NTS terminate in the thoracic cord (Doba and Reis, 1973, 1974). The time course of pulmonary edema following NTS lesions was similar to that after cerebral compression (Chen et al., 1973). Moreover, the edema in both instances was associated with increases in systemic arterial pressure. Both systemic hypertension and pulmonary edema after NTS lesions were prevented by prior treatment with phentolamine and by adrenalectomy (Doba and Reis, 1973, 1974; Nathan and Reis, 1975), indicating that, as with cerebral compression, the activation of α-adrenergic receptors mediated the response.

The difficulty in explaining the pulmonary edema resulting from NTS lesions is that there is only a doubling of systemic arterial pressure and peripheral vascular resistance after NTS lesions (Reis, 1981; Talman et al., 1981). The extent to which the rise in systemic arterial pressure is transmitted to the left atrium and then to the pulmonary capillaries where most of the fluid exchange in the lung occurs is not clear. Left atrial pressures greater than 25 mm Hg have been reported to result in alveolar pulmonary edema following cerebral compression probably is the result of activation of sympathetic vasomotor mechanisms at the level of medulla oblongata or cervical spinal cord. In further support of this conclusion, electrical stimulation of the spinal cord at C7 to C8 caused pulmonary edema (Chen et al., 1973); the edema was also prevented by ganglion blockade, α-adrenergic blockade, and sympathectomy (Chen et al. 1973, 1976).

FIGURE 2. Changes of arterial blood pressure and heart rate after cerebral compression with saline. Control cerebral compression (part A); rapid intravenous injection of norepinephrine, 1 mg/kg (part B); spinal compression at C7 (part C); slow cerebral compression (part D); rapid cerebral compression in adrenalectomized (part E), decerebrate (part F), spinal-transected (part G), and vagotomized (part H) animals. Tracings for all parts: top, arterial blood pressure; middle, heart rate; and bottom, signal indicating the time to achieve maximal cerebral compression or drug injection. Note the similar pattern of pressor responses in parts A, B, C, E, F, and H. (From Chen et al., 1973.)
edema (Guyton and Lindsay, 1959), which is a characteristic feature of neurogenic pulmonary edema. However, previous studies have not examined the relationship between the degree of systemic hypertension and the rise in pulmonary capillary hydrostatic pressure, and whether the rise in capillary pressure is, in fact, responsible for the edema.

Nonhemodynamic mechanisms also may have contributed to the edema formation after NTS lesions. A recent study by Simon (unpublished observation) suggested a contribution of the NTS in regulating lung fluid balance, and perhaps lung vascular permeability to protein. Bilateral lesions of NTS increased pulmonary lymph flow (i.e., a measure of the net transvascular fluid filtration rate) without significant changes in lymph-to-plasma protein concentration ratio and pulmonary hemodynamics.

The sites in the medulla responsible for the systemic hypertension (and, presumably, the pulmonary edema that results from the severe systemic hypertension) induced with the Cushing or cerebral ischemic response have been localized by Reis' group (Dampney et al., 1979). The area extends caudally from the level of the medial portion of the inferior olivary nucleus to the level of entry of the facial nerve (Dampney et al., 1979). The nucleus reticularis parvocellularis and nucleus gigantocellularis are located in this region. The medullary sites responsible for the systemic hypertension appear to be independent of the cardiovascular area which mediates the bradycardia also associated with the Cushing response (Dampney et al., 1979).

Other medullary areas may also play an important role in the development of neurogenic pulmonary edema. Destruction of the A1 noradrenergic neurons of the caudal ventral lateral medulla of rabbits either electrolytically or by local injection of the neurotoxin kainic acid resulted in systemic arterial hypertension, elevated plasma vasopressin concentration, and fulminant pulmonary edema (Blessing et al., 1981, and 1982). A1 neurons are thought to inhibit tonically the activity of the vasopressin-secreting neuroendocrine cells in the supraoptic and paraventricular nuclei through hypothalamic projections (Blessing et al., 1982). A1 neurons do not project to the spinal cord (Blessing et al., 1981, 1982). The neurogenic pulmonary edema occurring after lesion of A1 noradrenergic neurons may, therefore, have a vasopressin-dependent component. The A1 neurons also innervate the preoptic area of the hypothalamus (Day et al., 1980), and lesions of the preoptic area produce pulmonary edema (Gamble and Patton, 1953), as will be discussed below.

In summary, lesions of specific medullary sites result in pulmonary edema. Whether these areas are involved in the clinical form of fulminant neurogenic pulmonary edema is unknown. An important feature of the pulmonary edema occurring from medullary lesions is the association of the edema with systemic hypertension. However, it is unclear whether a rise in pulmonary capillary hydrostatic pressure secondary to the systemic hypertension is responsible for the edema formation. In addition, the nature of the edema induced by medullary lesions (i.e., whether due to high permeability or to increased capillary hydrostatic pressure) is not apparent from previous studies.

**Hypothalamus**

Unlike the medulla, the hypothalamus does not appear to be essential for the development of pulmonary edema after cerebral compression. Decerebration did not prevent the systemic arterial pressor response and pulmonary edema after rapid cerebral compression in rats, whereas sympathectomy or cervical spinal section prevented these changes (Chen et al., 1973). However, discrete hypothalamic lesions can directly result in pulmonary edema formation. Gamble and Patton (1951, 1953) observed pulmonary edema in rats after electrolytic lesions in the lateral preoptic area of the hypothalamus. Maire and Patton (1956a, 1956b) demonstrated that pulmonary edema could be consistently produced after a midline lesion dorsal to the optic chiasm. Sympathetic efferents were responsible for the edema following the preoptic lesions because cervical spinal transection prevented the edema, whereas vagotomy was ineffective (Maire and Patton, 1956a, 1956b).

Bilateral sectioning of the splanchnic nerves also prevented the edema induced by preoptic lesions (Maire and Patton, 1956a, 1956b). Since the edema was associated with marked reductions in liver and spleen weights, it may have been due to an intense sympathetic-mediated splanchnic vasoconstriction by the splanchnic nerves, a shift of blood volume to the lungs, and a resultant increase in pulmonary capillary hydrostatic pressure.

Prior midline lesions of the caudal hypothalamus prevented the pulmonary edema induced by preoptic lesions (Maire and Patton, 1956a, 1956b), which led these workers to conclude that the edema was the result of impulses arising from caudal hypothalamic structures that are normally held in abeyance by the preoptic region. This so-called "edemagenic center" was shown to lie in the rostral hypothalamus 2 mm caudal to the preoptic region (Maire and Patton, 1956a, 1956b). Destruction of the descending pathways from the rostral hypothalamus also prevented the pulmonary edema resulting from preoptic lesions (Maire and Patton, 1956a, 1956b). However, the concept of an "edemagenic center" remains controversial as Reynolds (1963) was unable to produce pulmonary edema with thermal lesions of the preoptic region. Stimulation studies of discrete hypothalamic sites have not been made to localize the sites of "edemagenic" impulses.

Although the concept of the hypothalamic "edemagenic center" remains vague, it is clear that these centers can modulate the degree of pulmonary edema. Doba and Reis (1974) showed that the pulmonary edemagenic effect of medullary NTS lesions in rats was eliminated by prior midcollicular decerebration. Moreover, lesion or stimulation of specific hypothalamic sites elicited the release of adreno-
medullary catecholamines (Folkow and von Euler, 1954; Nathan and Reis, 1975), which may contribute to increases in pulmonary capillary hydrostatic pressure and thereby act to increase extravascular lung water content (Minnear et al., 1981). The response to lesion of the anterior hypothalamus associated with fulminant pulmonary edema is shown in Figure 3. Although pulmonary vascular pressures were not recorded, there was an early large rise in systemic arterial pressure. Pulmonary edema associated with large increases in systemic arterial pressure and lesion of the alveolar epithelial lining was also induced by injection of an alkaloid aconitine directly into the anterior hypothalamus of rats (Minnear and Connell, 1981), supporting a hypothalamic mechanism in the response.

**Vagal Mechanisms**

Bilateral vagotomy resulted in pulmonary edema in the guinea pig and rabbits (Farber, 1957; Borison and Kovacs, 1959). The edema was not due to aspiration of the tracheal and gastric secretions, because these animals were intubated and artificially ventilated (Borison and Kovacs, 1959). Neither was the edema due to a sympathetic discharge, because transection of the spinal cord at the cervical level did not prevent the vagotomy-induced pulmonary edema (Borison and Kovacs, 1959). Discrete lesions of the dorsal vagal nuclei also resulted in pulmonary edema (Borison and Kovacs, 1959), indicating that specific vagal neurones were involved. Although this study suggests that damage to vagal nuclei causes a form of neurogenic pulmonary edema, its hemodynamic basis is not known because pulmonary vascular pressures were not monitored.

Reichsman’s (1946) review of the literature on the pathogenesis of pulmonary edema following bilateral vagotomy concluded that the edema was the result of either disturbances in pulmonary hemodynamics or laryngeal and airway spasms secondary to the vagotomy; unfortunately, our understanding of this form of edema has not improved since that time. Luisada and Sarnoff (1946) demonstrated that parasympatholytic drugs and atropine enhanced the pulmonary edema resulting from volume overloading, possibly because of pulmonary hemodynamic alterations such as a greater increase in pulmonary blood volume induced by blocking the vagal activity. On the other hand, Lorber (1939) observed that lung edema following bilateral vagotomy in the rat, guinea pig, and rabbits was associated with intense respiratory obstruction due to laryngeal and airway spasms. Vagotomy below the recurrent laryngeal nerve did not cause pulmonary edema or these airway changes (Lorber, 1939). When respiratory obstruction was added in a group of rats, the degree and rapidity of edema in this group was comparable to that occurring after vagotomy (Reichsman, 1946), suggesting that airway obstruction was responsible for the vagotomy-induced pulmonary edema. Severe regional airway obstruction may result in hyperinflation and markedly negative intrathoracic pressure in adjacent unobstructed lung regions due to an interdependent or tethering effect between adjacent lung segments (Permutt, 1979). This may increase the transcapillary filtration pressure in the hyperinflated regions; thus, it is possible that the edema is the result of the severe bronchomotor changes associated with the vagotomy.

In summary, disruption of vagal activity by vagotomy or by lesion of vagal nuclei in the medulla has been shown to induce pulmonary edema in the guinea pig, rat, and rabbit. It is unclear, however, whether the edema is the result of pulmonary hemodynamic alterations or severe airway constriction.

### Factors Initiating Central Nervous System Responses: Ischemia vs. Distortion

Medullary ischemia and brain stem distortion are believed to be the two essential factors that activate the sympathetic and medullary vagal centers during intracranial hypertension, (Forster, 1943; Rodbard and Saiki, 1952; Thompson and Malina, 1959). Both stimuli lead to the characteristic Cushing response (i.e., arterial hypertension and decreased heat rate) by activating the medullary vagal and sympathetic centers.

Cushing (1901) explained the systemic arterial hypertension after intracranial hypertension on the basis of decreased medullary blood flow and the resultant ischemia of medullary centers. Medullary perfusion decreases because intracranial pressure approaches the level of systemic arterial pressure, i.e., the cerebral perfusion pressure decreases below the threshold for cerebrovascular autoregulation so that the blood flow is reduced in direct proportion to the reduction in perfusion pressure (Malik et al., 1977). Rodbard and Saiki (1952) challenged Cushing's idea in studies in which the rate and magnitude...
of the rise of systemic arterial pressure were shown to be greater during intracranial hypertension than during cerebral ischemia induced by 100% nitrogen breathing. Moreover, the increase in systemic arterial pressure produced by anoxia did not prevent further increases in systemic arterial pressure after the elevation of intracranial pressure (Rodbard and Saiki, 1952). Therefore, the brain stem distortion leading to the discharge of medullary neurons may be a more potent stimulus for the Cushing response than cerebral ischemia.

Summary of Central Nervous System Pathways

Lesion of anatomically discrete centers in the medulla results in pulmonary edema, but the basis of the edema remains unclear—that is, whether the edema is the result of increased pulmonary capillary pressure or of increased lung vascular permeability. Little information exists on the role of specific medullary sites in regulating pulmonary hemodynamics and transvascular fluid and protein exchange. However, the pulmonary edema induced by medullary lesions is the result of sympathetic nervous system activation and is associated with systemic arterial hypertension. Hypothalamic centers may also contribute to the edema formation, but they do not appear to be of primary importance when the edema occurs after activation of medullary centers. Vagal nuclei and pathways are also involved, although the mechanisms of this form of edema are poorly understood.

Efferent Innervation of Pulmonary Blood Vessels

Sympathetic and parasympathetic motor innervation of the pulmonary vasculature influences pulmonary vasomotor tone (Bergofsky, 1980). Therefore any alterations in autonomic efferent activity may increase or decrease pulmonary capillary hydrostatic pressure. In this context, it is important to review the autonomic control of the pulmonary vasculature and how alterations in the control mechanisms may lead to pulmonary edema.

Anatomical Evidence of Innervation

Nerve bundles are present in the media of pulmonary vessels of various species, including dogs, cats, and sheep (Hebb, 1969; Fillenz, 1970; Garland and Keatinge, 1982). The innervation is more prominent at branch points of the pulmonary arteries (Fisher, 1965; Hebb, 1969; Fillenz, 1970; Knight et al., 1981; Kay, 1983). The pulmonary arteries in which nerve fibers are seen range in diameter from 30–500 μm (Hebb, 1969). These arteries contain little and unevenly distributed smooth muscle compared to systemic arteries of the same diameter (Hebb, 1969; Fillenz, 1970). It is generally believed that pulmonary veins are less innervated than arteries (Hebb, 1969). The overall poor innervation of the pulmonary vasculature in comparison with systemic vasculature explains why sympathetic nerve acti-

vation (as with intracranial hypertension) causes a weak pulmonary vasoconstrictor response (Lloyd, 1973; Maron et al., 1979). Moreover, the connections between nerve and muscle fibers appear to be less direct in pulmonary arteries than the skeletal muscle arterioles (Fillenz, 1970; Knight et al., 1981; Kay, 1983). In the pulmonary circulation, the vesi-

cle-filled nerve terminals run along the outer edge of the media and often do not penetrate into the smooth muscle cells (Hebb, 1969; Fillenz, 1970; Kay, 1983). The physiological significance of this is not clear; it is possible that smooth muscle cells are activated primarily by the spread of electrical activity from the media.

Response of Sympathetic Nerve Stimulation

A sympathetic-mediated increase in pulmonary vascular resistance is most effectively demonstrated in isolated dog lungs perfused under conditions of constant blood flow and left atrial pressure (Maron et al., 1979). Kadowitz and Hyman (1973) noted a relationship between the stimulation frequency and the increase in pulmonary vascular resistance with the greatest increase in resistance occurring at 30 cps. Alpha-adrenergic mechanisms mediate pulmonary vasoconstrictor response because the response is inhibited by phentolamine (Kadowitz and Hyman, 1973). Pulmonary veins are the primary site of increased resistance after sympathetic activation and intracranial hypertension (Daly et al., 1970; Hakim et al., 1979; Maron et al., 1980). This was assessed by partitioning resistance across the pulmonary vascular bed (Maron et al., 1980) (Fig. 4). Therefore,

![Figure 4. Influence of elevated cerebrospinal fluid pressure (PcSF) and vasoactive drugs on upstream (left of vertical line) and downstream (right of vertical line) pressure drops in the pulmonary circuit. Stippled area represents control upstream and downstream pressure drops. P values compare stimulus-induced changes in upstream and downstream pressure drops with the respective control pressure drops. Horizontal bars represent SE of difference between stimulus-induced changes in upstream and downstream pressure drops and the control pressure drops. Note the greater constriction of the downstream vessels (veins) after elevated PcSF, histamine, epinephrine, and norepinephrine. (From Maron and Dawson, 1981.)](http://circres.ahajournals.org/)

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**Citations:**
- Bergofsky, 1980
- Hebb, 1969
- Fillenz, 1970
- Hakim et al., 1979
- Maron et al., 1979
- Kadowitz and Hyman, 1973
- Daly et al., 1970
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- Lloyd, 1973
- Maron et al., 1979
- Maron et al., 1980
- Hakim et al., 1979
- Maron et al., 1980
- Maron and Dawson, 1981

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**Key Terms:**
- Pulmonary edema
- Intracranial hypertension
- Sympathetic nervous system
- Pulmonary vasculature
- Anatomical evidence of innervation
- Autonomic control
- Cushing response
- Sympathetic-mediated increase in pulmonary vascular resistance
- Alpha-adrenergic mechanisms
- Hypothalamic centers
- Pulmonary veins
- Systemic arterial hypertension
- Medullary centers
- Vagal nuclei
- Anatomically discrete centers in the medulla.
pulmonary capillary hydrostatic pressure may increase due to postcapillary constriction.

Ingram et al. (1968) found that sympathetic nerve stimulation at 10 cps did not increase the vascular resistance in isolated-perfused dog lungs, whereas resistance increased with infusion of norepinephrine. Their failure to obtain an increase in vascular resistance with nerve stimulation could have been due to differences in the sites of action of norepinephrine released from sympathetic nerve endings vs. the infused norepinephrine.

The pulmonary vascular bed contains both α-constrictor and β-dilator adrenergic receptors (Bergofsky, 1980; Hyman et al., 1983). These receptors have been identified using specific pharmacological antagonists for these receptors. The α-adrenergic blocking agents, phenoxybenzamine or phentolamine, inhibit the pulmonary vasoconstrictor effects of norepinephrine and convert the vasoconstriction resulting from epinephrine to vasodilation (Bergofsky, 1980). The latter response is inhibited by propranolol (Bergofsky, 1980). These effects of stimulation of α- and β-adrenergic receptors are observed in isolated-perfused lungs of cats and dogs and in pulmonary vascular smooth muscle strips of cats, rats, and guinea pigs (Bergofsky, 1980). The α-adrenergic receptors of the pulmonary vasculature predominate over the β-adrenergic receptors (Bergofsky, 1980; Hyman et al., 1983); therefore, pulmonary vasoconstriction occurs in response to agents such as epinephrine that activate both sets of receptors (Bergofsky, 1980). This is similar to the response in kidney, muscle, and splanchnic circulations.

Intact animals have a wider variation in the pulmonary vascular resistance response to increased sympathetic activity than the isolated-perfused lung because pulmonary vasodilation occurs passively as a result of the sympathetic-induced increase in cardiac output (Daly and Hebb, 1966). However, some animals, such as the calf, have a potent pulmonary vasoconstrictor response to sympathetic stimulation perhaps because of greater smooth muscle content of their pulmonary arteries (Daly and Hebb, 1966).

The physiological role of adrenergic receptors in the normal lung is a subject of much speculation. The adrenergic receptors appear to modulate rather than mediate the degree of pulmonary vasomotor tone during stimuli such as hypoxia (Bergofsky, 1980). The pulmonary vasoconstrictor responses to hypoxia, histamine, angiotensin, epinephrine, and norepinephrine were enhanced by prior inhibition of β-adrenergic receptors with propranolol (Porcelli and Bergofsky, 1973; Porcelli et al., 1977; Cutaia and Porcelli, 1983). The inhibition of β-adrenergic receptors decreased the smooth muscle cAMP content, which may explain the increased pulmonary vasomotor tone in the presence of propranolol (Cutaia and Porcelli, 1983). Conversely, activation of β-adrenergic receptors with agonists may increase the cAMP content, which may prevent excessive increases in pulmonary vasoconstriction with pulmonary vasoactive stimuli such as hypoxia (Cutaia and Porcelli, 1983). Thus, changes in the activity of β-adrenergic receptors may modulate the degree of pulmonary vasomotor tone in response to various vasoactive stimuli.

Increased pulmonary vasomotor tone induced by sympathetic activation has implications in contributing to pulmonary edema formation by raising the pulmonary capillary hydrostatic pressure. A rise in the pulmonary capillary pressure is likely because the pulmonary veins constrict to a greater extent than the arteries after intracranial hypertension (Maron et al., 1980). Dauber and Weil (1983) have shown that sympathetic-mediated pulmonary vasoconstriction enhances the degree of edema after an increase in lung vascular permeability, supporting the supposition that increased sympathetic activity contributes to neurogenic pulmonary edema by raising the pulmonary capillary pressure.

Some investigators have argued that the primary effect of enhanced sympathetic activity is to decrease pulmonary vascular compliance, not to increase vascular resistance (Ingram et al., 1968; Aarseth et al., 1971; Pace et al., 1972). Decreased pulmonary vascular compliance must be considered as an integral part of the response to sympathetic stimulation. The purpose of this, as Vanhoutte et al. (1981) have pointed out, may be to "hasten the surge of blood to the left heart and contribute to the overall adjustment of total vascular capacity"; the implication of decreased vascular compliance in the development of neurogenic pulmonary edema is discussed subsequently under the heading, Pulmonary Vascular Compliance.

Cholinergic Efferents

The role of cholinergic efferent nerves found in the medial layer of pulmonary arteries and veins remains conjectural (Hebb, 1969; Kay, 1983). Intravenous injection of acetylcholine produces a short-lived pulmonary vasodilation, which becomes prominent if the bed is preconstricted by alveolar hypoxia or serotonin (Fritts et al., 1958). Vagal nerve stimulation also induces pulmonary vasodilation (Nandiwanda et al., 1983). The vasodilation may reduce the pulmonary capillary hydrostatic pressure.

The vasodilation induced by vagal stimulation and acetylcholine may be mediated by the action of acetylcholine on muscarinic receptors of pulmonary vascular smooth muscle or acetylcholine may act on adrenergic terminals to limit vasoconstriction by inhibiting norepinephrine release (Bergofsky, 1980). The release of vasoactive intestinal peptide from the vagus (i.e., a noncholinergic, nonadrenergic pathway) (Matsuzake et al., 1980; Kay et al., 1981) may also contribute to the pulmonary vasodilation induced by vagal stimulation. This appears to be the case in some peripheral vessels and in airways (Diamond and O'Donnell, 1979). Finally, the release of vascular smooth muscle relaxing substance(s) from the endothelium has been proposed as a factor in
the acetylcholine-induced pulmonary vasodilation (Furchgott and Zawadski, 1980).

Mechanisms of Neurogenic Pulmonary Edema

Recognition of species difference is important to understanding the mechanisms of neurogenic pulmonary edema. Cats (Hoff et al., 1981; Millen, 1983), guinea pigs (Borison and Kovacs, 1959), and rats (Chen et al., 1973) developed pulmonary edema after cerebral insults such as intracranial hypertension and head injury with a greater predictability than dogs (Maron and Dawson, 1979). The reasons for marked species differences are not known, but species that possess a greater pulmonary sympathetic innervation or innervation at specific sites (e.g., at arterial branch points or pulmonary veins) may have a greater predisposition to pulmonary vasoconstrictor and edema responses.

Intracranial hypertension has been used extensively as a model for studying neurogenic pulmonary edema; however, this insult is probably not the sole cause of the edema because the edema is so variable after intracranial hypertension. Pulmonary edema developed in only half of anesthetized, paralyzed cats after increasing intracranial pressure by intraventricular infusion of mock cerebrospinal fluid (CSF) to 150–200 torr for 30 minutes, whereas pulmonary edema never occurred when pressure was raised to 100 torr (Hoff et al., 1981). The cerebral perfusion pressure (CPP) (i.e., the difference between mean aortic and intracranial pressures) may be a more reliable indicator because pulmonary edema formation was more closely related to CPP than intracranial pressure (Hoff et al., 1981). The increase in extravascular lung water content was not evident at a CPP of 50 torr, but was marked at CPP of 20 or 0 torr (Fig. 5). Since cerebral perfusion is maintained at normal levels even at a CPP of 40–50 torr by autoregulation in cerebral vessels (Malik et al., 1977), pulmonary edema may develop only at low CPP values when there is clear evidence of cerebral ischemia.

The following section discusses the mechanisms that have been postulated to mediate neurogenic pulmonary edema.

Hemodynamic Mechanisms

Left Atrial Hypertension

Pulmonary edema after intracranial hypertension is often associated with left atrial hypertension (Theodore and Robin, 1976). The problem with this hypothesis is that left atrial pressures of over 50 torr are needed to produce the rapid fulminant pulmonary edema that is characteristic of neurogenic pulmonary edema (Sarnoff and Sarnoff, 1952; Guyton and Lindsay, 1959; Cheng, 1975). Marked left atrial hypertension of this severity has not been routinely documented after intracranial hypertension in experimental animals and patients (Harari et al., 1976; Theodore and Robin, 1976). Moreover, there does not appear to be a relationship between the degree of left atrial pressure response after intracranial hypertension and the pulmonary edema (Hoff et al., 1981; Millen and Glauser, 1983).

Despite these shortcomings, it is clear that when a marked increase in left atrial pressure does occur, a direct pulmonary endothelial injury results from a rise in the pulmonary capillary hydrostatic pressure (Fishman and Pietra, 1980). Rippe et al. (1984) demonstrated that a rise in pulmonary capillary pressure of 55 cm H$_2$O maintained for only 4 minutes increased the capillary filtration coefficient in isolated-perfused lungs. This suggests that a marked left atrial hypertension (even if transient!) increases pulmonary vascular permeability. The increase in permeability was short-lived, lasting 15 minutes (Rippe et al., 1984). The idea of a pressure-induced increase in vascular permeability is further supported by the observation that severe left atrial hypertension after injection of norepinephrine increases endothelial junctional permeability to tracer macromolecules (Bohn, 1966; Pietra et al., 1969; Hurley, 1977) and also increases pulmonary lymph protein clearance in sheep (Minnear et al., 1983).

Systemic Arterial Hypertension

The left atrial hypertension discussed in the previous section may be the result of severe systemic arterial hypertension. Cerebral compression in rats...
produced a marked systemic pressor response (mean arterial pressure increased to 400 torr) and a transient bradycardia (Chen et al., 1973, 1980, 1981; Chen and Chai, 1974). These changes were associated with massive pulmonary edema that was not prevented by adrenalectomy or decerebration (Chen et al., 1973; Chen and Chai, 1974). Bilateral cervical vagotomy inhibited the bradycardia but had little effect on the systemic pressor response or the pulmonary edema formation (Chen et al., 1973; Chen and Chai, 1974). However, both hypertension and edema were prevented by α-adrenergic blockade (Chen et al., 1973; Chen and Chai, 1974). It was concluded that the edema was the result of intense sympathetic-mediated systemic arterial hypertension with the impulses originating in the medulla, followed by severe left atrial hypertension and pulmonary capillary hypertension. Unfortunately, left atrial and pulmonary capillary pressures were not monitored to determine the extent of the pressure rise and whether this rise in pressure was sufficient to explain the edema. An increase in pulmonary capillary pressure due to increased venous return was ruled out as a factor responsible for the pulmonary edema because regulating venous return during intracranial hypertension did not prevent the edema (Chen et al., 1980).

Sarnoff and Sarnoff (1952) have also championed the idea of pulmonary edema induced by left atrial hypertension, which they called "neurohemodynamic pulmonary edema." These workers believed the pulmonary edema to be the result of neurally mediated vasoconstriction events occurring in the systemic circulation. Injection of thrombin and fibrinogen into the cisterna magna of dogs resulted in an increase in left atrial pressure averaging 60 torr and a fulminant pulmonary edema (Fig. 6). The increases in pulmonary vascular pressures were associated with systemic arterial hypertension (Fig. 6). Left atrial hypertension and pulmonary edema were not prevented by vagotomy or bilateral sympathectomy to the level of the 5th thoracic ganglia, but sympathectomy beyond this point prevented the responses. There was a correlation between the increase in left atrial pressure and the pulmonary edema (Sarnoff and Sarnoff, 1952). The basis of the systemic and pulmonary hemodynamic alterations occurring with intracisternal fibrinogen and thrombin injection, however, may be independent of intracranial hypertension because increased intracranial pressure induced by other means in dogs did not induce a similar severe left atrial hypertension or pulmonary edema (Brash and Ross, 1970; Maron and Dawson, 1979). The observations of the Sarnoffs (1952) may be due to other factors, such as direct stimulation of medullary neurons by thrombin and other clotting factors (Cameron and De, 1949; McKinney et al., 1983) and thrombin-induced cerebral vasospasm (White et al., 1980).

Hoff and associates (1981) have examined the effect of systemic arterial hypertension in cats by preventing the intracranial hypertension-induced rise in systemic arterial pressure. Blood was withdrawn during systemic hypertension to regulate the level of arterial pressure (Fig. 4). Pulmonary edema still developed in this preparation, indicating that systemic arterial hypertension was not a requirement. Therefore, nonhemodynamic mechanisms during increased sympathetic activity (e.g., direct permeability effects) may also be important in the development of neurogenic pulmonary edema.

**Pulmonary Vasomotor Changes**

**Pulmonary Venous Constriction.** A sympathetic-mediated pulmonary venoconstriction and the consequent rise in pulmonary capillary pressure has been proposed as a hemodynamic mechanism causing pulmonary edema (Theodore and Robin, 1976; Pe-
Intracranial hypertension or sympathetic nerve stimulation increases postcapillary resistance to a greater extent than the precapillary resistance (Hakim et al., 1979a; Maron et al., 1980); therefore, pulmonary venoconstriction can be invoked as a leading cause of neurogenic pulmonary edema. This important edemagenic role of pulmonary venoconstriction is supported by the finding that a sympathetic-induced rise in pulmonary venous pressure markedly enhanced the degree of pulmonary edema after an increase in lung vascular permeability induced by oleic acid infusion in dogs (Dauber and Weil, 1983). The development of neurogenic pulmonary edema may similarly require an increase in lung vascular permeability associated with a sympathetic-mediated pulmonary venoconstriction. A small increase in pulmonary capillary pressure greatly enhances extravascular fluid accumulation in the event of an increase in pulmonary vascular permeability (Fig. 7). This can occur because of an increase in the transcapillary filtration resulting from the increase in the interstitial oncotic pressure (Taylor, 1981).

**Pulmonary Arterial Constriction.** Sympathetic nerve stimulation and intracranial hypertension also lead to pulmonary arterial constriction (Hakim et al., 1979a; Maron et al., 1980). Pulmonary arterial constriction may result in pulmonary edema if the constriction is non-uniform such that the blood flow is shunted to nonconstricted regions of the lung and the capillary pressure is increased in these regions. The microvasculature in the perfused region would therefore be exposed to increased capillary pressure and shear stress, both of which may increase vascular permeability (Sutton and Larsen, 1979; Landolt et al., 1983). This mechanism has been proposed to explain the pulmonary edema seen at high altitude (Sutton and Larsen, 1979). Recent studies have shown that shunting of the entire cardiac output through a third of the pulmonary vascular bed resulted in an increase in pulmonary lymph flow and a large decrease in the lymph-to-plasma protein concentration ratio. This is an indication of ultrafiltration (a capillary hydrostatic pressure effect) rather than increased pulmonary vascular permeability (Landolt et al., 1983). Therefore, it is unlikely that a non-uniform arterial constriction alone is an adequate explanation for the increased permeability seen in neurogenic pulmonary edema. However, if increased permeability occurs as a result of other mechanisms, a rise in the capillary hydrostatic pressure (induced by arterial or venoconstriction) would amplify the degree of extravascular fluid accumulation (Fig. 7).

**Mechanisms of Pulmonary Vasomotion after Intracranial Hypertension.** Pulmonary vasoconstriction after intracranial hypertension is seen in goats, cats, and monkeys (Ducker and Simmons, 1968; Hessler and Cassin, 1977; Hoff et al., 1981), but is absent or variable in dogs and sheep (Lloyd, 1973; Maron et al., 1979; van der Zee et al., 1983). Species differences in the intensity of pulmonary vasoconstriction and the reversal of the constriction by increases in left atrial pressure and pulmonary blood flow (Maron et al., 1979) may account for the different results.

If the second factor just mentioned is correct, then pulmonary vasoconstriction will be seen only if left atrial pressure and pulmonary blood flow are controlled during intracranial hypertension. Maron and Dawson (1979, 1980) examined this question using the perfused dog left lower lobe preparation to eliminate the contribution of hemodynamic factors (i.e., left atrial pressure and pulmonary blood flow changes) and humoral factors (i.e., endogenously released vasoactive agents into the blood). The lung lobe and peripheral circulation remained neurally intact because stellate ganglia stimulation produced increases in lobar and systemic vascular resistances. Increasing the intracranial pressure to 140 torr increased the systemic vascular resistance but did not change lobar vascular resistance, indicating the absence of neurally mediated pulmonary vasoconstriction (Maron and Dawson, 1979, 1980). However, cats and primates, which have more brisk pulmonary vasoconstrictor responses to sympathetic nerve stimulation than dogs (Ducker and Simmons, 1968; Brashear and Ross, 1970; Hoff and Nishimura, 1978), demonstrate an active pulmonary vasoconstrictor response after intracranial hypertension.

The perfusion of the left lower lobe with the dog's own venous blood resulted in a 34% increase in PVR after intracranial hypertension in contrast to perfusion with donor blood (Maron and Dawson, 1979). The increase in PVR was inhibited by occluding the adrenal vein, by phentolamine (an α-adrenergic antagonist), and by adrenalectomy (Maron and Dawson, 1979), suggesting that it was due to catecholamine release from adrenals. Pulmonary vasoconstriction also has not been observed in previous studies in pump-perfused dog lungs after...
intracranial hypertension (Lloyd, 1973), presumably because the lungs were perfused with donor blood. Although the results from the dog studies cannot be extrapolated to species with accentuated pulmonary vasoconstrictor responses to sympathetic stimulation and intracranial hypertension, they do indicate that adrenal medullary release of catecholamines following intracranial hypertension is as important a mediator of pulmonary vasoconstriction as stimulation of sympathetic efferents to the vascular smooth muscle.

**Pulmonary Vascular Compliance**

A sympathetic-mediated decrease in pulmonary vascular compliance may be another important determinant of the magnitude of rise in pulmonary capillary pressure. A relatively small increase in pulmonary blood volume due to shifting of blood from peripheral veins [following constriction of systemic veins (Stein et al., 1983)] may result in a greater increase in pulmonary capillary pressure in a pulmonary vascular bed with a decreased compliance (Fig. 8). Previous studies have demonstrated an increase in pulmonary capillary blood volume in dogs following a rise in CSF pressure of 100–200 torr (Stein et al., 1983). They have also shown that shifting of blood to the pulmonary circulation is associated with the development of pulmonary edema (Maire and Patton, 1956a, 1956b). The increase in pulmonary blood volume in a bed with a reduced vascular compliance due to sympathetic stimulation may contribute to edema formation by producing a larger increase in pulmonary capillary hydrostatic pressure (Fig. 8).

**Ventricular Compliance.** Although left ventricular compliance has not been measured after head injury or intracranial hypertension, it probably decreases as the sympathetic nerve activity increases. Because of decreased ventricular compliance, any increase in ventricular blood volume due to increased venous return or peripheral vascular resistance would result in an amplification of the left ventricular end-diastolic and left atrial pressures. This may explain why pulmonary edema is observed after medullary lesions in the face of relatively small increases in systemic arterial pressure (Doba and Reis, 1973).

**Bradycardia.** The bradycardia that occurs with intracranial hypertension (see Mechanisms of Bradycardia, below) may be another cardiac factor contributing to neurogenic pulmonary edema. Severe bradycardia occurring in the face of systemic vasoconstriction and increased venous return may result in excessive left ventricular filling, and thus produce large increases in left atrial and pulmonary capillary hydrostatic pressures.

**Mechanisms of Bradycardia.** An increase in the intracranial pressure to the level of systemic arterial pressure in dogs produced bradycardia (Kuo et al., 1972; Krasney and Koehler, 1976). Vagotomy or atropine reversed the bradycardia (Kuo et al., 1972; Chen and Chai, 1976). Both cerebral compression and cerebral ischemia have been implicated in the response. A decrease in cerebral perfusion pressure in the isolated-perfused head of the dog induced without cerebral compression produced a delayed-onset bradycardia (Kuo et al., 1972; Chen and Chai, 1976), suggesting a direct role for cerebral ischemia in the response. Other studies, however, have shown an immediate bradycardia upon raising intracranial pressure to 130 mm Hg (Kuo et al., 1972). The issue of whether ischemia or brain stem distortion is responsible for the heart rate response remains unresolved.

The bradycardia resulting from cerebral compression or ischemia is independent of the systemic pressor response and appears to be mediated by CNS structures, since it occurred after intracranial hypertension in instances when there was no change or even a decrease in the systemic arterial pressure (Kuo et al., 1972; Chen and Chai, 1976). Moreover, preventing the rise in arterial pressure after intracranial hypertension did not abolish cardiac slowing (Kuo et al., 1972; Chen and Chai, 1976). Sinoaortic denervation also did not inhibit the bradycardic response (Kuo et al., 1972). Another indication that CNS mechanisms contribute directly to the heart rate changes was the finding that a similar degree of intracranial hypertension on the left side of the skull produced more cardiac arrhythmias than the right side (Krasney and Koehler, 1976). This is probably due to the asymmetrical activation of the CNS autonomic pathways. Therefore, the bradycardia...
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after intracranial hypertension appears to be initiated independently in the medulla, rather than by a peripheral baroreceptor feedback.

Stimulation of the nucleus tractus solitarius or nucleus ambiguous consistently produced cardiac slowing, with the effect being more prominent in the nucleus ambiguous (Chen and Chai, 1976; Levy and Martin, 1981). A lesion of the dorsal motor nucleus of the vagus as well as vagotomy abolished the bradycardia after stimulation of these nuclei (Chen and Chai, 1976; Levy and Martin, 1981), indicating that the efferent pathway is via the vagus. The cardiac slowing associated with intracranial hypertension may be mediated by activation of the nucleus tractus solitarius and nucleus ambiguous in the medulla oblongata leading to the activation of vagal efferent pathways. Sympathetic pathways may also be involved in the bradycardia response to intracranial hypertension because the tachycardia was unmasked after bilateral cervical vagotomy in dogs subjected to intracranial hypertension (Krasney and Koehler, 1976).

Summary of Mechanical Factors

Neurogenic pulmonary edema is associated with transient systemic arterial and left atrial hypertension. The extent to which pulmonary capillary hydrostatic pressure is affected by these changes cannot be ascertained from previous studies.

Increases in left atrial pressure of greater than 50 mmHg that injure the pulmonary endothelium are not commonly observed in experimental conditions such as intracranial hypertension. However, when severe left atrial hypertension does occur, as after intracisternal injection of thrombin, it may lead to the rapid development of fulminant edema by a pressure-induced increase in pulmonary vascular permeability. Rapid fluid accumulation in the interstitial spaces does not occur in the normal lung after small elevations in left atrial pressure that have been observed during intracranial hypertension; there are "safety" factors that reduce edema formation, i.e., decreased interstitial oncotic pressure, increased interstitial hydrostatic pressure, increased pulmonary lymph flow, and decreased the fraction of the interstitium that excludes albumin (Taylor, 1981). The small rise in pulmonary capillary pressure, however, may be an important determinant of pulmonary edema if lung vascular permeability is increased by other mechanisms (Taylor, 1981); therefore, the small pressure rise may play an essential permissive role in the development of neurogenic pulmonary edema.

Permeability Alterations

Neurogenic Influences on Transcapillary Fluid and Protein Fluxes

Sympathetic activity controls pulmonary transvascular fluid and solute exchange by regulating the number of open capillaries, and also by adjusting the pre- to post-capillary resistance ratio and thereby increasing the capillary pressure (Fig. 1) (Rosell, 1980). Another less understood factor in sympathetic control of tissue fluid balance may involve direct control of endothelial permeability. This could occur by alterations in the numbers and dimensions of endothelial "pores" (Rosell, 1980). Nerves are often in intimate contact with capillaries and small arteries and veins, where most of the fluid and protein exchange normally occurs (Jancso et al., 1967; Alekseyev and Chernukh, 1973). The following sections discuss the experimental evidence.

Evidence in Pulmonary Vascular Bed. At present, circumstantial evidence supports a direct permeability increase as a mechanism of neurogenic pulmonary edema. Injection of thrombin and fibrinogen into the cisterna magna (fibrin was localized in the fourth ventricle in the area of the vagal nucleus) resulted in pulmonary edema (within 5–10 minutes) in rats and rabbits (Cameron, 1948; Cameron and De, 1949). The protein concentration of airway edema fluid ranged from 4.7–5.5 g/dl (Cameron and De, 1949) suggesting an increase in the permeability of the alveolar-capillary membranes. The small increases in systemic arterial pressure of 20 to 50 mmHg could not account for the substantial protein-rich pulmonary edema. Intracerebral fibrin or fibrin degradation products may be involved in mediating the pulmonary edema because intracisternal injections of plasma, serum, heparinized blood, thrombin, or fibrinogen alone had no effect on lung water content (Cameron and De, 1949). Fibrin may act by occluding the apertures of the 4th ventricle, thereby increasing CSF pressure (Cameron and De, 1949). However, CSF pressure increases within 5 minutes are likely to be small due to the compliance of the CSF space (Sullivan et al., 1978). Another possibility is that fibrin and/or its degradation products stimulate medullary sympathetic neurons (McKinney et al., 1983), which, in turn, somehow increase pulmonary microvascular permeability.

Intracranial hypertension induced in sheep by mock CSF, saline, or blood resulted in an increased pulmonary lymph flow while the lymph-to-plasma protein concentration ratio did not change. These changes have been interpreted as indicating increased vessel wall permeability (Bowers et al., 1979; van der Zee, 1980; Peterson et al., 1983). However, this may not be the case. The increase in permeability may be small because raising the left atrial pressure after a period of intracranial hypertension produced a further rise in lymph flow and a concomitant decrease in the lymph-to-plasma protein concentration ratio (Jones et al., 1982; van der Zee et al., 1983), suggesting a normal sieving of proteins by the microvascular barrier (Fig. 9).

A recent study (Peterson et al., 1983) has proposed that endogenous opioids (e.g., endorphins) are im-
important in increasing lung vascular permeability and extravascular lung water content after intracranial hypertension. This conclusion is based on smaller lymph flow and lymph protein clearance responses observed after intracranial hypertension in sheep pretreated with naloxone (an opiate-receptor antagonist) (Fig. 10). The naloxone-treated sheep also did not develop pulmonary edema. The basis of this protective effect is not clear. Endorphins may directly increase lung vascular permeability. These substances are co-transmitters in noradrenergic vesicles of sympathetic nerves (Wilson et al., 1980), and thus would be released during nerve stimulation.

Stellate ganglion stimulation, which was used to simulate the sympathetic activation induced by intracranial hypertension, produced increases in pulmonary transvascular fluid and lymph protein fluxes that were not associated with changes in pulmonary vascular pressures or blood flow (Hakim et al., 1979b). A direct effect of sympathetic nerve stimulation in increasing pulmonary microvascular permeability cannot be invoked at this time because increased fluid filtration rate resulting from a sympathetic-mediated increase in vascular surface area may have occurred.

An increase in sympathetic discharge emanating from the CNS results in pulmonary edema such as the pulmonary edema seen after epileptic seizures induced by bicuculline in rats (Kiesseling et al., 1981). In sheep, the edema appears to be the result of a rise in pulmonary capillary pressure induced by the seizure rather than a permeability increase (Simon, 1982). It remains to be established whether there is a neuronal influence on microvascular permeability and whether this is an important mechanism of neurogenic pulmonary edema.

Evidence in Other Vascular Beds. Rosell (1980) has been a main proponent of the concept that sympathetic nerves regulate microvascular permeability. Sympathetic nerve stimulation in the abdominal fat pad of dogs resulted in an increase in vascular permeability at the time when blood flow to the tissue was reduced (Intaglietta and Rosell, 1974). The capillary filtration coefficient (CFC), a function of the surface area available for fluid exchange and capillary permeability, was increased after sympathetic nerve stimulation to the same extent as with histamine and bradykinin, both of which are known to increase permeability (Rosell, 1980). In contrast, substances such as prostaglandin E1 (PGE1), acetylcholine, and isoproterenol (agents that do not increase permeability) produced maximum vasodilation but only a moderately increased CFC (Rosell, 1980). The clearance of locally injected 125I sodium iodide was also examined to differentiate between vascular surface area and permeability (Rosell, 1980). Sympathetic nerve stimulation reduced 125I sodium iodide clearance, probably as a result of decreased local perfusion and decreased surface area, while CFC was increased (Rosell, 1980). Al-

![Figure 9](http://circres.ahajournals.org/)

**Figure 9.** Effects of increased pulmonary lymph flow induced by left atrial hypertension (Pla) on lymph-to-plasma protein concentration ratio. • = response in sheep subjected to transient period of intracranial hypertension (Pic); ○ = response in normal sheep. Steady state values of each of eight animals are shown at baseline, after intracranial hypertension, and during left atrial hypertension. In all cases, the increase in pulmonary lymph flow is associated with a decrease in the lymph-to-plasma protein concentration ratio, indicative of a capillary hydrostatic (ultrafiltration) effect. (From van der Zee et al., 1983.)

![Figure 10](http://circres.ahajournals.org/)

**Figure 10.** The relationship between pulmonary lymph flow response and cardiac output. The regression line was calculated from the four groups of sheep that had no postmortem evidence of pulmonary edema (○). However, the four sheep with an ICP of 100 mm Hg (○) had postmortem evidence of pulmonary edema. (From Peterson et al., 1983.)

125I sodium iodide was also examined to differentiate between vascular surface area and permeability (Rosell, 1980). Sympathetic nerve stimulation reduced 125I sodium iodide clearance, probably as a result of decreased local perfusion and decreased surface area, while CFC was increased (Rosell, 1980). Al-
though the evidence remains controversial, one explanation for the data is that the increase in CFC in adipose tissue represents an increase in microvascular permeability. Other tenable explanations are that: (1) contribution of the more permeable venous segments of the microvasculature is increased during sympathetic nerve stimulation, and (2) blood flow is redistributed during sympathetic nerve stimulation to vessels with higher permeabilities.

Electrical stimulation of the locus coeruleus in the Rhesus monkey produced an increase in permeability of cerebral microvessels to water despite a reduction in cerebral blood flow (Raichle et al., 1975, 1976), suggesting that the central noradrenergic system in the locus coeruleus contributes to the regulation of blood-brain barrier permeability to water (Hartman, 1973). Bilateral cervical sympathetic stimulation also increased water permeability, although to a lesser extent than stimulation of central noradrenergic nerves (Grubb et al., 1978). The proposed mechanism for the neurally mediated increase in cerebrovascular permeability is shown in Figure 11. These studies are inconclusive because regional increases in vascular surface area and redistribution of blood flow may independently increase transvascular water movement without affecting hydraulic conductivity (Preskorn et al., 1982). Alterations in the selectivity of the cerebral microvascular barrier to solutes of varying molecular radii have not been examined.

**Mechanisms of Neurogenic Alterations in Fluid and Protein Fluxes**

The notion that an increase in pulmonary microvascular permeability is mediated by increased sympathetic activity or secondary release of mediators (e.g., endorphins) remains an attractive hypothesis because neurogenic pulmonary edema has often been reported to occur in the face of relatively small changes in pulmonary hemodynamics (Harari et al., 1976; Theodore and Robin, 1976; Fein et al., 1979; Fein and Rackow, 1982). The morphological basis of the increase in endothelial permeability may be the intrinsic contractility of endothelial cells (Majno et al., 1969) which enables the cells to change size and shape. Endothelial shape change resulting from inhibition of actin polymerization in the cell with cytochalasin B was associated with an increased pulmonary vascular permeability to proteins (Shasby et al., 1982), suggesting that an endothelial permeability change can occur by an alteration in cell shape. Another mechanism of increased permeability is via contraction of pericytes which may be influenced by the autonomic nervous system (Krogh, 1929). The pericytic cells in the lung are strategically situated at sites surrounding the small fluid-exchanging microvessels (Sims and Westfall, 1982).

**β-Adrenergic Modulation of Vascular Permeability**

Several studies have proposed that β-adrenergic receptors modulate the endothelial permeability to proteins in peripheral and pulmonary microvessels (Svensjo et al., 1977; Joyner et al., 1979; Persson et al., 1979; Grega et al., 1980; Prasad et al., 1982). The increase in vascular permeability induced by histamine or bradykinin in skin (Svensjo et al., 1977), in skeletal muscle (Prasad et al., 1982), and in hamster cheek pouch (Joyner et al., 1979) was inhibited by β-adrenergic agonists isoproterenol and terbutaline. Terbutaline also prevented the increase in lung water content occurring after a histamine challenge (Persson et al., 1979). Isoproterenol was 10-fold more potent than terbutaline in decreasing vascular permeability after histamine in hamster cheek pouch and in guinea pig skin vessels (Joyner et al., 1979; Svensjo et al., 1977). Morphological studies using tracers indicated that the β-agonists prevented the edema in the skin following histamine or bradykinin infusions by reducing permeability of the interendothelial junctions (Joyner et al., 1979; Svensjo et al., 1977).

Joyner et al. (1979) quantified leakage of fluorescein isothiocyanate dextran (molecular weight 150,000) by determining the number of leakage sites per cm² appearing in the cheek pouch after a topical application of PGE₁, PGE₂ produced dose-dependent increases in the leakage sites, but pretreatment

**Figure 11.** The proposed neurally mediated mechanism for regulation of brain water permeability. The hypothesis is based on four assumptions: (1) water preferentially leaves capillary through specialized pores or tight junction; (2) capillary endothelial cells and/or the investing pericytes are contractile; (3) capillary endothelial cells and pericytes receive functional innervation from noradrenergic neurons which produce endothelial or pericyte contraction upon stimulation, and produce relaxation upon being blocked; and (4) mechanical distortion of specialized pores or tight junction changes brain water permeability. α-Adrenergic blockade with phentolamine decreased the permeability-surface area product (PS) and increased the cerebral blood flow (CBF), whereas sympathetic activation increased PS and decreased CBF (from Raichle et al., 1976).
with terbutaline reduced the number (Fig. 12). PGE, also increased blood flow to the region, but this was not affected by terbutaline (Joyner et al., 1979), suggesting that inhibition of the permeability increase by isoproterenol was a direct action on the endothelial cell. The mechanism of this effect of β-adrenergic agonists is unknown; inhibition of histamine- or bradykinin-induced contractions of endothelial cells at the level of the cytoskeleton is a possibility.

The role of β-adrenergic mechanisms in regulating pulmonary microvascular permeability has not been critically examined. It is incorrect to extrapolate findings from systemic vessels. Peresson et al. (1979) reduced the degree of histamine-induced edema in guinea pig lung by pretreatment with β-adrenergic agonists. β-Adrenergic blockade in sheep with propranolol increased pulmonary lymph flow and did not affect the baseline lymph-to-plasma protein concentration ratio (Hakim et al., 1981); however, the increased lymph flow may have resulted from increased vascular surface area rather than increased vessel wall permeability. If the hypothesis that β-adrenergic activation decreases lung vascular permeability is correct, pulmonary edema would be more likely to develop in the presence of inhibition of β-receptors; however, this question has not been examined.

**Pulmonary Microembolization**

Occlusion of pulmonary vessels by microemboli may be another contributing factor in neurogenic pulmonary edema. Platelet count and fibrinogen concentration were decreased after cerebral insults (Kaufman et al., 1980), suggesting intravascular platelet aggregation and microthrombi. Platelet aggregation may occur as a result of increased epinephrine concentrations reported after intracranial hypertension and head injury (Beckman and Iams, 1979; Patscheke, 1980).

Plasma thromboplastin concentration is increased after head injury (Kaufman et al., 1980), possibly due to entry of brain tissue thromboplastin into the circulation through the cerebral venous system. Thromboplastin activates the extrinsic coagulation cascade and may contribute to the embolization of pulmonary vessels with fibrin (Malik, 1983). Pulmonary intravascular microthrombi should be considered as a potential mechanism of neurogenic pulmonary edema because intravascular coagulation increases pulmonary vascular permeability (Malik, 1983).

Pulmonary edema developed within 20 minutes after air microembolism that was induced during the process of raising intracranial pressure (Malik, 1977; Peterson et al., 1980), whereas pulmonary edema does not occur this rapidly with embolization alone (Malik, 1980). It is possible, therefore, that a combination of both microembolism and intracranial hypertension are required to produce the characteristic fulminant protein-rich neurogenic pulmonary edema. This hypothesis takes into account the known permeability-increasing effect of pulmonary microembolism (Malik, 1983) and the pulmonary vasoconstrictor effect of intracranial hypertension (Maron et al., 1980).

**Lymphatic Failure**

Since an impairment of the pulmonary lymphatic pump can theoretically result in pulmonary edema (Taylor, 1981), it is possible that constriction of lymphatics induced by sympathetic activation (McHale and Roddie, 1983) influences the development of neurogenic pulmonary edema. Norepinephrine injection in intact sheep did not increase pulmonary lymph flow, whereas there were large increases in pulmonary arterial and left atrial pressures to 50 and 40 torr, respectively (Minnear et al., 1983a). The lungs were grossly edematous, suggesting that lymphatic insufficiency occurring in conjunction with the pressure-induced increase in vascular permeability contributed to the edema (Minnear et al., 1983a). In the normal lung, the lymph flow attains a plateau as the capillary filtration in-
Neurogenic pulmonary edema may also occur independently of the large increases in left atrial pressures, suggesting that a nonhemodynamic mechanism (possibly a direct permeability increase) is involved. The evidence supporting this hypothesis is circumstantial. Some studies suggest that permeability of systemic microvessels is modulated by β-adrenergic mechanisms, suggesting that alterations in sympathetic activation may influence pulmonary vascular permeability.

Neurogenic pulmonary edema after cerebral insults develops rapidly and is protein rich. The edema appears to be the result of interactions among several factors: (1) a rise in the pulmonary capillary hydrostatic pressure, (2) an increase in endothelial permeability induced by the rise in the capillary hydrostatic pressure and/or non-hemodynamic mechanisms (e.g., release of mediators), (3) pulmonary microembolization secondary to intravascular thrombosis and platelet aggregation, and (4) lymphatic obstruction due to sympathetic activation.

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