

NEUROGENIC PULMONARY OEDEMA

Amit Agrawal¹, Jake Timothy², Lekha Pandit³, Anand Kumar⁴, G.K. Singh⁵, R. Lakshmi⁶

B.P. Koirala Institute of Health Sciences, Department of Surgery¹, Dharan, Nepal. Leeds General Infirmary, Department of Neurosurgery², Leeds, U.K. K.S.Hegde Medical Academy, Department of Neurology³, Mangalore, India. B.P. Koirala Institute of Health Sciences, Departments of Surgery⁴, Orthopedics⁵ and Medicine⁶. Dharan, Nepal.

Neurogenic pulmonary oedema (NPO) usually occurs following severe central nervous system (CNS) injuries (i.e. as a consequence of grand mal seizures, subarachnoid haemorrhage, intracranial bleeding, severe head injury or sometimes following spinal cord injuries). However, the pathogenesis of NPO is not entirely clear. In the majority of cases, early or classic symptoms of pulmonary oedema are evident from several minutes up to several hours after CNS damage. Dyspnoea, chest pain, bloody expectoration are observed shortly after consciousness disorders, although NPO may occasionally be diagnosed on the basis of chest x-ray in patients with no clinical symptoms. Tachypnoea, tachycardia, rales without any changes in cardiac system are usually observed during physical examination. The ailments withdraw quickly in the majority of patients, who may require oxygen therapy at most.

Key words: Pulmonary oedema, neurogenic, neurogenic pulmonary edema

Eur J Gen Med 2007;4(1):25-32

INTRODUCTION

Pulmonary oedema may be defined as a set of clinical symptoms resulting from over hydration of pulmonary tissue impairing its compliance (1,2). There are many causes responsible for the development of this pathology; the most frequent of them include the diseases of cardiovascular, hypervolaemia, acute or chronic renal diseases, pneumonia and other infections, chemical, physical and biological injuries of the lungs, the inhalation of toxic gases or the swallowing of volatile hydrocarbons with subsequent aspiration (e.g. paraffin oil). The development of pulmonary oedema in the setting of a sudden neurological event is termed neurogenic pulmonary edema (NPO) (1-3). NPO is a serious and life-threatening complication following several lesions of the central nervous system. We discuss the aetiology and pathogenesis of NPO based on the available literature.

Aetiology

Neurogenic pulmonary oedema (NPO) may develop in the acute stage of patients who have sustained sudden neurological injury including subarachnoid hemorrhage (SAH),

(4-8) intracranial hemorrhage, (9-11) head injury, (9,12,13) ischemic stroke, (14,15) acute hydrocephalus, (16,17) and seizures (8,9,18-20).

Neurogenic pulmonary oedema is seen in up to 50% of patients who have suffered a severe brain insult such as trauma, subarachnoid hemorrhage, stroke, or status epilepticus (21). NPO is one of the most serious complications of high-grade subarachnoid hemorrhage (SAH) that lead to poor clinical outcome and seen in up to 10-20% of cases with aneurysmal subarachnoid hemorrhage (5,6,22-24). In one study pathological or radiological evidence for NPO was found in up to 67% with fatal aneurysmal SAH (25). Similarly, in another study NPO was evident in 92% patients with aneurysmal SAH who died before arrival at the hospital (6).

Pathophysiology

NPO was first described by Shanahan in 1908 in 11 patients with epilepsy (26). After that, many authors associated various kinds of CNS damage leading to the increase of intracranial pressure in patients without

Correspondence: Dr. Amit Agrawal
Assistant Professor in Neurosurgery, Department of Surgery, B.P. Koirala Institute of Health Sciences
Dharan, Nepal
Tel: 9772552555/2047, Fax: 97725520251
E-mail: dramitagrawal@gmail.com

primary changes in heart and lungs with subsequent pulmonary oedema (18,27-29). However, despite a number of clinical and experimental studies, the mechanisms leading to NPO are not fully understood (30).

Hypothalamic injury

NPO is thought to be related to a central sympathetic discharge as a consequence of acute hypothalamic dysfunction and medullary ischemia that can be induced by the intracranial stress due to rupture of an intracranial aneurysm or any other insult (8,22-25,31). Rapid elevation in intracranial pressure which stimulates the hypothalamus or subthalamic nucleus directly or indirectly, results in increased sympathetic activity, elevation of serum catecholamine level, and concurrence of NPO (22). This mechanism of NPO has been confirmed by the selective damage of hypothalamus (8,22-24). The most important factor affecting the occurrence of NPO is the severity of provoking event (22).

Deformation of medulla oblongata

In some studies, deformation of the medulla oblongata by the ruptured vertebral artery aneurysm was found to be the cause of NPO. Deformation of medulla oblongata evokes the sympathetic tone and catecholamine surge. The dorsal nucleus and solitary nucleus of the vagus, located in the cat dorsal medulla oblongata, function as suppressors of sympathetic activity and the A1 (adrenergic) region located at the ventrolateral site of the medulla oblongata stimulates the dorsal nucleus and the solitary nucleus. Therefore, functional loss of the ventrolateral site of medulla oblongata evokes the catecholamine surge and sympathetic vasoconstriction (32-35).

Role of pulmonary vasculature

The contraction of pulmonary vessels may be caused by the stimulation of sympathetic system or it may well be an effect of massive release of catecholamines following CNS damage (18,36). The consequence of this fact is the elevation of systemic and pulmonary pressure and a simultaneous decrease of blood flow in the aorta (27,37). This increase of blood volume in pulmonary vessels and simultaneous elevation of pressure in pulmonary circulation leads to the damage of pulmonary endothelium and consequently, to a permeability defect (1,2,27,30). Neurally induced transient rise in intravascular pressure may damage the endothelium causing protein-

rich plasma to escape into the interstitial and alveolar spaces. In humans, elevated pulmonary artery wedge pressures have been observed only in few cases. Pulmonary oedema can also develop with normal pulmonary artery wedge pressures, suggesting a neural-mediated, pressure-independent influence on capillary permeability (7,11,27,31,38).

Spinal cord injury and NPO

NPO though uncommon can occur in patients with spinal cord injuries and an important co-factor of morbidity and mortality. NPO edema is characterized as an acute, protein-rich lung edema occurring shortly after spinal cord injury. Yet, the precise pathogenetic mechanisms, incidence and clinical significance of development of neurogenic pulmonary oedema remain unclear. There is evidence that the motor cortex is involved in cardiovascular adjustments associated with somatic motor activity, as it has functional connections with the CVL medulla, a brainstem region critically involved in the control of blood pressure and the regulation of plasma catecholamine levels (39-42).

The caudal ventrolateral medulla (CVL) sends projections to the spinal intermediolateral nucleus, where preganglionic neurons take control of heart and blood vessels (T2 segment) and adrenal medulla (T8 segment). Injury to the middle thoracic spine cord can probably justify the occurrence of haemodynamical disturbances and pulmonary oedema (39).

Role of neurotransmitters

Nathan and Reis observed that arterial hypertension, elevated peripheral resistance, and diminished cardiac output were reversed to normal by alpha-receptor blockade with phentolamine. Also, these authors demonstrated that bilateral adrenalectomy, adrenal demedullation or adrenal denervation performed prior to producing the lesions in the hypothalamus prevented the development of arterial hypertension and pulmonary oedema, as well as the changes in peripheral resistance, cardiac output, and body temperature. Glazer and Ross observed noradrenergic (NE) bulbospinal innervation to midthoracic sympathetic preganglionic nuclei in the rat thoracic cord by immunocytochemical localization of dopamine-beta-hydroxylase, a specific NE antigen (43,44).

The rapid development of pulmonary edema that may occur in the rabbit after the

intracisternal injection of fibrinogen and thrombin has classically been considered to result from a cholinergic mediated increase in vascular permeability. The conclusion for this study revealed that vagotomy had no protective effect but instead appeared to increase the amount of oedema development for a given degree of pulmonary hypertension (45).

Widdicombe reported that the trachea-bronchial vasculature is controlled by adrenergic, cholinergic and peptidergic nervous mechanisms. This author showed that sympathetic nerves release norepinephrine and neuropeptide Y (both of which are constrictor agents) while parasympathetic nerves release acetylcholine and usually vasoactive intestinal polypeptide (both of which are vasodilators). Activation of pulmonary C-fiber receptors may cause a powerful vasodilatation, mainly via sympathetic motor nerves, and cardiac and chemoreceptor reflexes also influence airway vascular tone. Sensory nerves in the airway mucosa are responsible for local axon reflexes and these nerves contain neuropeptides such as substance P, neurokinins A and B, and calcitonin gene-related peptide (all these neuropeptides are powerful vasodilators) (46).

The neuropeptide Y is believed to be an important mediator in neurogenic pulmonary oedema, responsible for the increased pulmonary vascular permeability and differences in receptor modulation. Injection of ibotenic acid, a glutamate agonist, into the ventral medullary raphe (VMR), especially the nucleus raphe magnus, of the rat produced respiratory failure and death following a predictable course of events, but pre-treatment with PPP, a sigma receptor agonist, or scopolamine, a muscarinic cholinergic antagonist, prevented pulmonary failure and death. Based on these results, preliminary pharmacological studies suggest that disruption of glutamatergic and cholinergic mechanisms mediates the lethal pulmonary phenomenon. Imaizumi et al. had always investigated the role of the caudal ventrolateral medulla (CVL) in rats (47-49).

The use of neuro-excitatory (L-glutamate) and neuro-inhibitory (muscimol) agents into the depressor region of the CVL of anesthetized rabbits indicated that the sympathoinhibitory neurons in the CVL medulla tonically suppress the activity of sympathetic preganglionic neurons controlling myocardial contractility as well as peripheral vasomotor tone, and that dysfunction of these

medullary neurons could underlie some forms of experimental hypertension (50). It was proposed that neurogenic pulmonary edema is a functional disturbance provoked by adverse stimuli from outside the lungs and that in the rat the primary afferent fiber is essential to the production of this entity based on the effect of neonatal capsaicin treatment (to destroy unmyelinated C-fibers) on neurogenic pulmonary-oedema from fluid-percussion brain injury in the adult-rat (51).

It was suggested that when endothelium derived relaxing factor (EDRF) release is inhibited during massive sympathetic nervous system activity, pulmonary vascular resistance is markedly increased, which causes the right ventricle to fail. The reduced right ventricular output maintains pulmonary microvascular pressure below levels required for oedema development (52). Another study revealed that intracranial hypertension elicits vasoconstriction of the systemic and pulmonary resistance and capacitance vessels and the major cause of volume and pressure loading in the pulmonary circulation is acute left ventricular failure resulting in a dramatic decrease in aortic flow (53).

The intrathecal injection of endothelins to conscious rats was found to cause respiratory arrest. The increase of pulmonary vascular permeability and oedema induced by endothelin-1 are due to an intense pulmonary vasoconstriction mediated by alpha-adrenoceptors, following the release of catecholamines in response to the activation of endothelin receptor in the spinal cord. This central phenomenon seems to be reflexogenic, including the involvement of primary afferent C-fibers and spinal cord ascending fibers to the brain (54).

Hamdy et al. (55) used fibrinogen and thrombin injected into the rat's cisterna magna to induce neurogenic pulmonary edema. They observed that neuropeptide Y has a relationship to the high protein concentration ratio or to increased pulmonary vascular permeability, which consequently may contribute to the development of neurogenic pulmonary oedema in rats.

ECG changes

Many patients developed QT prolongation, a finding that is often observed in subarachnoid hemorrhage and other sudden neurologic events (56). The release of catecholamines during the ictus may induce this conduction disturbance and cause cardiac pump failure (7). Mayer et al. described echocardiographic

evidence of reduced left ventricular function, border line CK-MB elevation, various ECG changes and persistent T wave inversions in their series of five patients with SAH and NPO (7).

Chest X-ray

Chest radiographs in patients with neurogenic pulmonary oedema usually do not identify features that could distinguish hydrostatic from increased permeability as the mechanism of pulmonary edema (57).

Clinic

Clinical symptoms of NPO may be observed a few seconds or minutes after the seizure (1,27,30). Symptoms can subside quickly, and therefore, some of the patients do not display all the expected symptoms after being transported to hospital. Patients with pulmonary oedema usually complain of difficulties in breathing, cough, chest pain and bloody expectoration of medium intensity. Physical examination usually reveals tachypnoea, tachycardia, rales above the lungs, without evident signs of cardiac insufficiency (1,2,11). In the case of intensive after-load, considerable burdening of left ventricle and its failure may be observed. Left ventricular failure develops as a result of beta-adrenergic activation, negative inotropic CNS effect on the heart (increased tension of vagus nerve and/or poor function of alpha-adrenergic system) (2,30). The elevation of body temperature and moderate leucocytosis may also be observed. Chest x-ray reveals the features of pulmonary oedema, which diminishes within the following 24–48 hours (1,2,58).

Differential diagnosis

Other cardiogenic, neurogenic, or toxic causes of pulmonary oedema should be excluded. In obscure cases the presence of toxins such as cocaine, amphetamines or opiates should be screened. Family and patient interviews and a physical examination to exclude intoxication as a cause of illness should not be forgotten. Viral pneumonia should also be excluded (59). Differentiation of neurogenic pulmonary oedema from simple fluid overload or post-extubation oedema may be difficult if not impossible in trauma patients or immediately following surgery. Therefore, the diagnosis of neurogenic pulmonary oedema is obtained by exclusion. Its cause remains controversial but probably involves a combination of factors associated with

hydrostatic oedema and factors associated with permeability oedema without diffuse alveolar damage. The cellular mechanisms that cause capillary leakage are also not well understood. Modifications in autonomic pathways are probably the cause of sudden, significant increases in microvascular pressure in the lungs, particularly in the pulmonary venules. This leads to reduced venous outflow, which in turn causes pulmonary capillary and arterial hypertension (60). In addition, there are probably direct effects of various mediators that cause leakage of vascular endothelial cells and cell junctions. Patients may present with varying degrees of dyspnea, tachypnea, and cyanosis shortly after suffering the brain insult. These signs and symptoms decrease and disappear rapidly in most cases. Conventional chest radiography demonstrates the presence of bilateral, rather homogeneous airspace consolidations, which predominate at the apices in about 50% of cases. More recently, some authors have observed the predominance of diffuse pulmonary oedema that is rather inhomogeneous in distribution (21). Radiologic findings in neurogenic pulmonary edema also disappear within 1–2 days, thereby confirming the absence of any associated diffuse alveolar damage (60).

Management

According to the literature, two therapeutic points are the most important in the control of the problem: the first is respiratory support and the second is the haemodynamic improvement. This knowledge is of great importance due to the need to learn more about the subject and how to solve the life-threatening complication in patients with neurogenic pulmonary oedema (39). The treatment of NPO is non-specific and it is based on oxygen therapy, diuretics, possibly antibiotics, bronchodilating agents and digitalis preparations, just as in the case of pulmonary oedema of different aetiology. Soon after the introduction of such treatment, clinical improvement can be observed. In spite of this, mechanical ventilation and appropriate monitoring of pressure in pulmonary microvessels may occasionally be necessary (1). It should be remembered, however, that positive end-expiratory pressure (PEEP) may be the cause of intracranial pressure increase (58). Animal studies suggest that alpha-adrenergic blockers can be useful in the prevention of NPO (58). Circulatory and renal diseases as well as toxic pulmonary damage are to taken into account during differentiation diagnostics and other causes of pulmonary oedema is to

be ruled out (61,62).

Studies showing that it is possible to pharmacologically increase the rate of alveolar fluid reabsorption suggest that it might eventually be possible to devise therapies designed to promote alveolar fluid reabsorption and consequently improve gas exchange and oxygenation in patients with alveolar flooding. In this regard, interest has been expressed in the possible use of beta 2-adrenergic agonist therapy in such patients (63). The observation that edema resolution in NPO appears to be naturally accelerated by an endogenous beta 2-adrenergic agonist raises questions as to whether it will be possible to make clinically useful improvements in the rate of recovery from alveolar flooding in patients with NPO or other forms of edema in which alveolar liquid clearance (ALC) has been found to be endogenously accelerated (64).

Whether knowing the precise cause in individual patients is important, is a matter of conjecture. Our patient had moderate pulmonary hypertension and a low-normal cardiac index, suggesting a degree of left ventricular impairment. However, PAWP was 18 mm Hg at its highest, a borderline figure for the diagnosis of cardiogenic pulmonary oedema.

In addition, the introduction of inotropic support did not affect pulmonary artery pressure, PAWP or oxygenation, again suggesting that left ventricular dysfunction was not a major component of the pathophysiology. As well as being a direct threat to life, the severe hypoxia that results from NPO may worsen the neurological injury (65).

Positive pressure ventilation and the use of high levels of PEEP are frequently required and may worsen cerebral perfusion (and therefore outcome) by reducing cardiac output and by impeding cerebral venous drainage. Any therapy that substantially improves oxygenation and allows a reduction in mean airway pressure and duration of mechanical ventilation may improve survival and neurological recovery (65). The results of a study suggest that an increase in alveolar epithelial sodium transport produced by endogenous epinephrine may play a significant role in promoting the rapid recovery. First, Sakuma and coworkers have recently found that terbutaline increases ALC in resected human lung lobes, indicating that alveolar epithelial sodium transport is capable of being upregulated by beta 2 stimulation in humans.

The increase in ALC could be prevented with propranolol, a beta-adrenergic antagonist. Second, patients with NPO may exhibit elevated plasma and urinary catecholamine concentrations (1). Finally, NPO generally resolves relatively quickly (24 to 72 h) in patients who survive the initial CNS insult (1), suggesting that ALC may be upregulated. Taken together, these observations suggest that the ability to remove sodium and water from the airspaces might be upregulated in patients with NPO (66). NPO incidents are extremely rare after the seizures, particularly in children, but it should be kept in mind that these incidents have life-threatening potential (18,29). Although clinical course of NPO is usually dramatic but short, the cases of 'fulminant' pulmonary oedema leading to patient's death are also described (1,2,62). Mechanical ventilation in the prone position improves oxygenation in ~60% of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (65,67). It is still generally felt, however, that prone ventilation is an appropriate therapy that may benefit subgroups of patients or improve outcome if used early (68). Although prone ventilation is generally safe, the presence of traumatic brain injury (TBI) is a relative contraindication; there is anecdotal evidence that in such patients, with reduced intracranial compliance, prone positioning increases intracranial pressure. There are experimental data that show an increase in intracranial pressure during partial prone positioning in patients with TBI (69). In patients with poor grade SAH, a high proportion will have raised intracranial pressure (70).

Conclusions

Neurogenic pulmonary oedema is an uncommon complication of severe neurological injury. There have been many attempts to understand the pathophysiological events which can cause such devastating injury systemically. Although, in general it has been associated with a discharge of sympathetic activity, the above review concludes that there are many potential mechanisms that may cause NPO, likewise, potential treatments will only come with further understanding of these mechanisms.

REFERENCES

1. Colice GL. Neurogenic pulmonary edema. *Clin Chest Med* 1985;6:473-89
2. Colice GL. Neurogenic pulmonary edema. *Am Rev Respir Dis* 1984;130:941-8

3. Simon RP. Neurogenic pulmonary edema. *Neurol Clin* 1993;11:309-23
4. Ezura M, Takahashi A, Ogasawara K, Yoshimoto T. Intra-aneurysmal GDC embolization followed by intrathecal tPA administration for poor-grade basilar tip aneurysm. *Surg Neurol* 1997;47:144-8
5. Fujimura M, Seki H, Sugawara T, Tomichi N, Oku T, Higuchi H. Anomalous internal carotid artery anterior cerebral artery anastomosis associated with fenestration and cerebral aneurysm. *Neurol Med Chir* 1996;36:229-33
6. Schievink WI, Wijdicks MD, Parisi JE, Piepgras DG, Whisnant JP. Sudden death from aneurysmal subarachnoid hemorrhage. *Neurology* 1995;45:871-4
7. Mayer SA, Fink ME, Homma S, et al. Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. *Neurology* 1994;44:815-20
8. Pender ES, Pollack CJ. Neurogenic pulmonary edema: case reports and review. *J Emerg Med* 1992;10:45-51
9. Ducker TB. Increased intracranial pressure and pulmonary edema: Clinical study of 11 patients. *J Neurosurg* 1968 28: 112-7
10. Weisman SJ. Edema and congestion of the lungs resulting from intracranial hemorrhage. *Surgery* 1939;6:722-9
11. Carlson RW, Schaeffer RJ, Michaels SG, et al. Pulmonary edema following intracranial hemorrhage. *Chest* 1979;75: 731-4
12. Solander S, Ulhoa A, Vinuela F, et al. Endovascular treatment of multiple intracranial aneurysms by using Guglielmi detachable coils. *J Neurosurg* 1999;90:857-64
13. Wohns RN, Tamas L, Pierce KR, et al. Chlorpromazine treatment for neurogenic pulmonary edema. *Crit Care Med* 1985; 13:210-11
14. Cohen JA, Abraham E. Neurogenic pulmonary edema: a sequela of non-hemorrhagic cerebrovascular accidents. *Angiology* 1976; 27:280-92
15. Harari A, Rapin M, Regnier B, et al. Normal pulmonary-capillary pressures in the late phase of neurogenic pulmonary oedema [letter]. *Lancet* 1976;1:494
16. Findler G, Cotev S. Neurogenic pulmonary edema associated with a colloid cyst in the third ventricle: case report. *J Neurosurg* 1980;52:395-98
17. Braude N, Ludgrove T. Neurogenic pulmonary oedema precipitated by induction of anaesthesia. *Br J Anaesth* 1989; 62:101-03
18. Terrence CF, Rao GR, Perper JA. Neurogenic pulmonary edema in unexpected, unexplained death of epileptic patients. *Ann Neurol* 1981;9: 458-64
19. Ohlmacher AP. Acute pulmonary edema as a terminal event in certain forms of epilepsy. *Am J Med Sci* 1910;139:417-22
20. Bonbrest HC. Pulmonary edema following an epileptic seizure. *Am Rev Respir Dis* 1965;91:97-100
21. Ell SR. Neurogenic pulmonary edema: a review of the literature and a perspective. *Invest Radiol* 1991;26:499-506
22. Watanabe T, Sekiguchi K, Inoue A, Taniguchi Y, Sato S. Clinical evaluation of neurogenic pulmonary edema following acute stage of subarachnoid hemorrhage. *No Shinkei Geka* 1992;20:417-22
23. Di Giugno G, Rosa G. Neurogenic pulmonary edema during subarachnoid hemorrhage. *Minerva Anestesiol* 1998;64: 229-30
24. Kin H, Ogihara R, Tomita S, et al. Acute pulmonary edema following rupture of intracranial aneurysm. *Neurol Med Chir* 1981;1:313-20
25. Weir B. Pulmonary edema following fatal aneurysmal rupture. *J Neurosurg* 1978;49:502-7
26. Shanahan WT. Acute pulmonary edema as a complication of epileptic seizures. *NY Med J* 1908; 37:54-6
27. Theodore J, Robin ED. Speculations on neurogenic pulmonary edema (NPO). *Am Rev Respir Dis* 1976;113:405-11
28. Fein IA, Rackow EC. Neurogenic pulmonary edema. *Chest*, 1982; 81: 318-20
29. Lear GH. Neurogenic pulmonary oedema. *Acta Paediatr Scand* 1990;79:1131-3
30. Malik AB. Mechanisms of neurogenic pulmonary edema. *Circ Res* 1985;57:1-18
31. Yabumoto M, Kuriyama T, Iwamoto M, et al. Neurogenic pulmonary edema associated with ruptured intracranial aneurysm: case report. *Neurosurgery* 1986;19:300-04
32. Geiger H, Naraghi R, Schobel HP, Frank H, Sterzel RB, Fahlbusch R. Decrease of blood pressure by ventrolateral medullary decompression in essential hypertension. *Lancet* 1998;352(9126):446-9
33. Jannetta PJ, Segal R, Wolfson SK Jr: Neurogenic hypertension: etiology and

- surgical treatment. I. observations in 53 patients. *Ann Surg* 1985;201:391-8
34. Levi EI, Clyde B, McLaughlin MR, Jannetta PJ. Microvascular decompression of the left lateral medulla oblongata for severe refractory neurogenic hypertension. *Neurosurgery* 1998;43:1-9
 35. Ochiai H, Yamakawa Y, Kubota E. Deformation of the ventrolateral medulla oblongata by subarachnoid hemorrhage from ruptured vertebral artery aneurysms causes neurogenic pulmonary edema. *Neurol Med Chir* 2001;41:529-35
 36. Maron MB. A canine model of neurogenic pulmonary edema. *J Appl Physiol* 1985;59:1018-25
 37. Sarnoff SJ, Sarnoff LC. Neurohemodynamics of pulmonary edema. *Dis Chest* 1952;22:685-96
 38. Wray NP, Nicotra MB. Pathogenesis of neurogenic pulmonary edema. *Am Rev Respir Dis* 1978;118:783-6
 39. Filho MBL, Morandin RC, de Almeida AR, et al. Hemodynamic parameters and neurogenic pulmonary edema following spinal cord injury. *Arq Neuropsiquiatr* 2005;63(4):990-6
 40. Fontes RBV, Aguiar PH, Zanetti MV, Andrade F, Mandel M, Teixeira MJ. Acute neurogenic pulmonary edema: case reports and literature review. *J Neurosurg Anesthesiol* 2003;15:144-50
 41. Schwarz S, Schwab S, Keller E, Bertram M, Hacke W. Neurogenic impairment of cardiopulmonary function in acute cerebral lesions. *Nervenarzt* 1997;68:956-62
 42. Solokhin EV, Belova TS, Naumov MR, et al. Morphological changes in lungs of patients with spinal injuries died in hospital. *Sud Med Ekspert* 2000;43:17-9
 43. Nathan MA, Reis DJ. Fulminating arterial hypertension with pulmonary edema from release of adrenomedullary catecholamines after lesions of the anterior hypothalamus in the rat. *Cir Res* 1975;37:226-35
 44. Glazer EJ, Ross LL. Localization of noradrenergic terminals in sympathetic preganglionic nuclei of the rat: demonstration by immunocytochemical localization of dopamine-beta-hydroxylase. *Brain Res* 1980;185:39-49
 45. Bosso FJ, Lang SA, Maron MB. Role of hemodynamics and vagus nerves in development of fibrin-induced pulmonary edema. *J Appl Physiol* 1990;69:2227-32
 46. Widdicombe JG. Neural control of airway vasculature and edema. *Am Rev Resp Dis* 1991;143(Suppl):S18-S21
 47. Leal MB Filho, Morandin RC, Almeida AR, et al. Importance of anesthesia for the genesis of neurogenic pulmonary edema in spinal cord injury. *Neurosci Lett* 2005;373:165-70
 48. Carruth MK, Fowler AA, Fairman RP, Mayer DJ, Leichnetz GR. Respiratory-failure without pulmonary-edema following injection of glutamate agonist into the ventral medullary pappe of the rat. *Brain Res Bull* 1992;28:365-78
 49. Imaizumi T, Granata AR, Benarroch EE, Sved AF, Reis DJ. Contributions of arginine vasopressin and the sympathetic nervous system to fulminating hypertension after destruction of neurons of caudal ventrolateral medulla in the rat. *J Hypertens* 1985;3:491-501
 50. Drolet G, Chalmers J, Blessing W. Vasodepressor neurons in medulla alter cardiac contractility and cardiac output. *Hypertension* 1993;21:210-5
 51. Levasseur JE, Patterson JL, Garcia CI, Moskowitz MA, Choi SC, Kontos HA. Effect of neonatal capsaicin treatment on neurogenic pulmonary-edema from fluid-percussion brain injury in the adult-rat. *J Neurosurg* 1993;78:610-8
 52. Pilati CF, Maron MB, Bosso FJ. Role of EDRF in the cardiopulmonary dysfunction produced by massive sympathetic activation. *J Appl Physiol* 1995;78:1642-50
 53. Chen HI. Hemodynamic mechanisms of neurogenic pulmonary edema. *Biol Sig* 1995;4:186-92
 54. Poulat P, Couture R. Increased pulmonary vascular permeability and oedema induced by intrathecally injected endothelins in rat. *Eur J Pharmacol* 1998;344:251-9
 55. Hamdy O, Nishiwaki K, Yajima M, et al. Presence and quantification of neuropeptide Y in pulmonary edema fluids in rats. *Exp Lung Res* 2000;26:137-47
 56. Samuels MA. Neurally induced cardiac damage: definition of the problem. *Neurol Clin* 1993;11:273-92
 57. Aberle DR, Wiener KJ, Webb WR, et al. Hydrostatic versus increased permeability pulmonary edema: diagnosis based on radiographic criteria in critically ill patients. *Radiology* 1988;168:73-9
 58. Darnell JC, Jay SJ. Recurrent postical pulmonary edema: a case report and review of the literature. *Epilepsia* 1982;

- 23: 71-83
59. André Louis Gabry, Xavier Ledoux, Monique Mozziconacci and Claude Martin. High-Altitude Pulmonary Edema at Moderate Altitude (< 2,400 m; 7,870 feet): A Series of 52 Patients. *Chest* 2003;123:49-53
60. Smith WS, Matthay MA. Evidence for a hydrostatic mechanism in human pulmonary edema. *Chest* 1997;111:1326-33
61. Johnson SC, Darragh TM, Simon RP: Postical pulmonary edema requires pulmonary vascular pressure increases. *Epilepsia* 1996; 37:428-32
62. Rogers FB, Shackford SR, Trevisani GT et al: Neurogenic pulmonary edema in fatal and nonfatal head injuries. *J Trauma* 1995;39:860-8
63. Barker PM. Transalveolar Na⁺ absorption: a strategy to counter alveolar flooding? *Am J Respir Crit Care Med* 1994;150: 302-3
64. Lane SM, Maender KC, Awender NE, Maron MB. Adrenal Epinephrine Increases Alveolar Liquid Clearance in a Canine Model of Neurogenic Pulmonary Edema. *Am J Respir Crit Care Med* 1998; 158:760-8
65. Fletcher SJ, Atkinson JD. Use of prone ventilation in neurogenic pulmonary oedema. *Br J Anaesth* 2003;90:238-40
66. Sakuma TG, Okaniwa T, Nakada T, Fujimura NS, Matthay MA. Alveolar fluid clearance in the resected human lung. *Am. J. Respir. Crit Care Med.* 1994;150: 305-10
67. Tobin A, Kelly W. Prone ventilation it's time. *Anaesth Intens Care* 1999;27:194-201
68. Slutsky AS. The acute respiratory distress syndrome, mechanical ventilation and the prone position. *N Engl J Med* 2001;345: 610-11
69. Lee ST. Intracranial pressure changes during positioning of patients with severe head injury. *Heart Lung* 1989; 18: 411-4
70. Le Roux PD, Winn HR. Intracranial aneurysms and subarachnoid hemorrhage. Management of the poor grade patient. *Acta Neurochir (Wien)* 1999; 72 (suppl): 7-26