Arq Neuropsiquiatr 2005;63(4):990-996

HEMODYNAMIC PARAMETERS AND NEUROGENIC PULMONARY EDEMA FOLLOWING SPINAL CORD INJURY

An experimental model

Manoel Baldoino Leal Filho[1], Rosana C. Morandin[2], Amanda R. de Almeida[2], Elizabeth C. Cambiucci[2], Konradin Metze[4], Guilherme Borges[3], José Antonio Rocha Gontijo[2].

ABSTRACT - Neurogenic pulmonary edema is a serious and always life-threatening complication following several lesions of the central nervous system. We report an experiment with 58 Wistar-Hanover adult male rats. Two groups were formed: control (n=4) and experimental (n=54). The experimental group sustained acute midthoracic spinal cordinjury by Fogarty's balloon-compression technique containing 20µL of saline for 5, 15, 30 or 60 seconds. The rats were anesthetized by intraperitoneal (i.p.) sodium pentobarbital (s.p.) 60 mg/Kg. The quantitative neurological outcome was presented at 4, 24 and 48 hours from compression to characterize the injury graduation in different groups. Poor outcome occurred with 60 seconds of compression. Six animals died suddenly with pulmonary edema. Using the procedure to investigate the pulmonary edema during 60 seconds of compression, followed by decompression and time-course of 60 seconds, 20 rats were randomly asigned to one of the following groups: control (1, n=4, anesthetized by i.p. s.p., 60 mg/Kg but without compression) and experimental (2, n=7, anesthetized by i.p. xylazine 10 mg/Kg and ketamine 75 mg/Kg) and (3, n=9, anesthetized by i.p. s.p., 60 mg/Kg). The pulmonary index (100 x wet lung weight / body weight) was 0.395 ± 0.018 in control group, rose to 0.499 ± 0.060 in group 2, and was 0.639 ± 0.14 in group 3. Histologic examination of the spinal cord showed parenchymal ruptures and acute hemorrhage. Comparison of the pulmonary index with morphometric evaluation of edema fluid-filled alveoli by light microscopy showed that relevant intra-alveolar edema occurred only for index values above 0.55. The results suggest that the pulmonaryedema induced by spinal compression is of neurogenic nature and that the type of anesthesia used might be important for the genesis of lung edema.

KEY WORDS: spinal cord injury, neurogenic pulmonary edema, central nervous system lesions.

Parâmetros hemodinâmicos e edema pulmonar neurogênico após traumatismo raquimedular: modelo experimental

RESUMO - Edema pulmonar neurogênico é complicação séria e aumenta o risco de vida em pacientes com várias lesões do sistema nervoso central. Apresentamos uma experiência com 58 ratos Wistar machos e adultos. Foram formados dois grupos: controle (n=4) e experimental (n=54). O grupo experimental sofreu trauma raquimedular torácico médio com o cateter-balão de Fogarty contendo 20µL de salina por 5, 15, 30 ou 60 segundos de compressão. Os ratos foram anestesiados com pentobarbital sódico (p.s.), 60 mg/Kg intraperitoneal (i.p.). Foi investigada a relação entre a lesão medular e o tempo de compressão. A evolução neurológica foi quantificada e apresentada com 4, 24 e 48 horas da compressão para caracterizar a graduação da lesão nos diferentes grupos. A pior evolução ocorreu com 60 segundos de compressão. Seis animais morreram subitamente com edema pulmonar. Vinte ratos foram randomicamente distribuídos em um dos seguintes grupos: controle (1, n=4, anestesiados com p.s. i.p., 60 mg/Kg, mas sem compressão) e experimental (2, n=7, anestesiados com xilasina 10 mg/Kg e ketamina 75 mg/Kg) e (3, n=9, anestesiados com p.s. i.p., 60 mg/Kg). O índice pulmonar (100 x peso pulmonar / peso corporal) foi 0,395 ± 0,018 no grupo controle, 0,499 ± 0,060 no grupo 2, e 0,639 ± 0,14 no grupo 3. O exame histológico da medula espinhal mostrou rupturas no parênquima e hemorragia aguda. Comparando-se o índice pulmonar com o índice morfométrico através da microscopia óptica, evidenciou-se que ocorreu edema intra-alveolar relevante para índices acima de 0,55. A presente experiência sugere que o edema pulmonar induzido pela compressão medular é de natureza neurogênica e que o tipo de anestesia utilizada no experimento poderia ter participação na gênesis do edema pulmonar.

PALAVRAS-CHAVE: traumatismo raquimedular, edema pulmonar neurogênico, lesões do sistema nervoso central.

[1]Curso de Pós-graduação em Ciências Médicas, Doutorado em Neurologia; [2]Laboratório Hidro-Salino, Núcleo de Medicina e Cirurgia Experimental, Departamento de Clínica Médica; [3]Neurologia e [4]Anatomia Patológica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), São Paulo, SP, Brazil. This study was supported by grants from CNPq (500868/91-3) and (302189/2004-1), PRONEX (0134/97), CAPES and FAPESP (00/12216-8).

Received 14 April 2005, received in final form 6 July 2005. Accepted 26 August 2005.

Dr. Manoel Baldoino Leal Filho - Rua Thomaz Tajra 1222/300 - 64048-380 Teresina PI - Brasil. E-mail: manoelbaldoino@uol.com.br

Neurogenic pulmonary 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 elicited neurogenic pulmonary edema remain unclear[1]. The pulmonary alveolar-capillary barrier needs to satisfy two conflicting requirements: it must be extremely thin for efficient gas exchange and also strong enough to withstand the extremely high stress in the capillary wall when capillary pressure rises[2]. The strengh of the pulmonary blood-gas barrier on the thin side is attributable to the type IV collagen in the basement membranes[2-4]. However, when the wall stress rises to very high levels, ultrastructural changes occur in the barrier, a condition known as stress failure[2]. Pathophysiological conditions such as high-altitude pulmonary edema, neurogenic pulmonary edema, severe left ventricular failure, mitral stenosis, overinflation of the lung and others result in stress failure[3]. Recent experimental findings suggest that rapid changes in gene expression for extracellular matrix proteins and growth factors occur in response to increases in capillary wall stress[2].

In patients with spinal cord injuries respiratory complications are still an important cofator of morbidity and mortality. Fontes et al.[5] published cases of acute neurogenic pulmonary edema after several several seizure episodes followed by cranioplasty and subarachnoid hemorrhage due to a cavernoma. Additionally, these authors presented a literature review since 1990 of human cases of neurogenic pulmonary edema, which resulted in fourteen reports (21 cases) to be analysed[5].

Although different experimental animal models that simulate the traumatic spinal lesions seen in human have been described, in the present communication we have assessed the time-dependent repercussion of hemodynamic parameters, sensory and motor activities and pulmonary edema in an original experimental model of spinal cord injury in rats and also performed an extensive review of the literature about the subject.

METHOD

Fifty-eight male Wistar-Hannover rats, weighing between 300 and 350 g, were obtained from the University's breeding center. The general guidelines established by the Brazilian College for Animal Experimentation (COBEA) were followed throughout this study. The experiment design was previously approved by the Institutional Committee for Ethics in Animal Research. The rats were anesthetized with intraperitoneal sodium pentobarbital (60mg/kg body weight, i.p.) and the level of anesthesia was controlled by corneal reflex monitoring. In order to evaluate the effect of spinal cord injury on systolic (SBP) / diastolic (DBP) blood pressure (in mmHg) and heart rate (HR, in bpm) by means of a BESE polygraph, the right carotid artery of all animals was cannulated and they were randomly assigned to one of these groups:

1) Control (sham) group: four anesthetized rats were submitted to ligamentum flavum removal followed by insertion of Fogarty® catheter balloon (12-062-2F) into the dorsal epidural space 1 cm cranially to midthoracic levelwithout insufflations of the catheter and spinal cord compression (SC).

2) Experimental SC group 1: 23 anesthetized rats were submitted to the same surgical procedure as group 1 and suffered additional SC at midthoracic level by insufflations of 20 μL of saline solution into the balloon during 5, 15, 30 and 60 seconds, being evaluated 4-h after SC.

3) Experimental SC group 2: 17 anesthetized rats were submitted to the same surgical procedure as group 1 and suffered additional SC at midthoracic level by insufflations of 20 μl of saline solution into the balloon during 5, 15, 30 and 60 seconds, being evaluated 12-h after SC.

4) Experimental SC group 3: 14 anesthetized rats submitted to the same surgical procedure as group 1 and suffered additional SC at midthoracic level by insufflations of 20μL of saline solution into the balloon during 5, 15, 30 and 60 seconds, being evaluated 24-h after SC.

Subsequently the experimental group was submitted to time-course extradural compression. The animals were observed in a flat, barrier-free environment for spontaneous motor activity of the hind limbs according to Khan et al., which was scored as: (0) no movement in the hind limbs, no weight bearing; (1) barely perceptible movement of hind limbs, no weight bearing; (2) frequent movement of hind limbs, no weight bearing; (3) ability to support weight on hind limbs, may take one or two steps; (4) ability to walk with mild deficit; and (5) normal walking[6]. Also, the neural sensorial test was performed accordingly and scored as follows: (0) no reaction to foot pinch; (1) foot jerks without consistent withdrawal toward the body; (2) normal, rapid withdrawal of hind limb to body; and (3) hyperflexion of the hind limb, spastic shaking[6].

At the end of each blood pressure and heart rate recording, the rats were perfused by the left carotid artery saline containing heparin (2%) for 5 min under constant pressure. This was followed by perfusion with 0.1 M phosphate buffer (PB; pH 7.4) containing 4% (w/v) paraformaldehyde and 0.1 M sucrose with overnight fixation by freezing 24 hours later the spinal cord and the lung were removed and analysed.

The pulmonary edema was evaluated by the pulmonary index (100 x wet lung weight / body weight). For that, 20 rats weighing between 300 and 350 g were used. The experimental groups were submitted to a compression of 60 seconds, followed by decompression and a ti-

me-course of 60 seconds. The animals were randomly asigned to one of the following groups: control (1, n=4, anesthetized by i.p. s.p., 60mg/Kg but without compression) and experimental (2, n=7, anesthetized by i.p. xylasine 10mg/Kg and ketamine 75mg/Kg) and (3, n=9, anesthetized by i.p. s.p., 60mg/Kg). After the experiment the animals were sacrificed using an overdose of anesthesia and the lungs were harvested and the pulmonary index was calculed. The lungs were fixed by immersion for 24 hours in 4% formaldehyde, dehydrated and embedded in paraffin and 5µm haematoxylin-eosin stained sections were examined by light microscopy.

For quantitative evaluation of the pulmonary sections there were randomly selected 10 microscopic fields (objective magnification 40 x) per case and counted the percentage of alveoli which were at least partially filled with eosinophilic edema fluid. The morphometric index of edema fluid-filled alveoli was evaluated by light microscopy in paraffin sections.

Statistical analysis – All data are reported as means ± SEM. Data obtained over time were analyzed using appropriate ANOVA. *Post hoc* comparisons between selected means were done with Bonferroni's contrast test when initial ANOVA indicated statistical differences between experimental groups. Comparisons involving only two means within or between groups were done using Student's *t* test. A p value < 0.05 was considered significant.

RESULTS

The basal (systolic and diastolic) blood pressure and heart rate levels in the control and all experimental groups were similar. In the control sham-operated group, the heart rate was constant during the whole experiment, whereas the systolic and diastolic blood pressuredecreased significantly during the experiment (SBP from: 129.2 ± 4.7 mmHg to 115 ± 5.0 mmHg, p=0.03; and DBP from: 100.0 ± 1.0 mmHg to 87.5 ± 5.0 mmHg, p=0.001). In the pentobarbital anesthetized rats with SC, peak heart rate rose from 212.0 ± 19.0 bpm to 258.0 ± 22.0 bpm (Fig 1) and fell afterwards below baseline level (160.0 ± 45.0 bpm, p=0.0002). In these experiments, systolic arterial pressure doubled the baseline pressure (116.0 ± 14.0 mmHg) during spinal cord compression (232.0 ± 33.0 mmHg) (see Fig 1) and decreased afterwards to still elevated levels (148.0 ± 14.0 mmHg, p=0.0001). The diastolic pressure showed similar statistically significant changes, and increased from baseline levels of 91.4 ± 10.7 mmHg to 131.4 ± 8.0 mmHg during SC compression, dropping to 116.0 ± 6.0 mmHg after compression (p=0.0001).

Figure2 and 3 exemplify spinal cord injury and lung specimens from the control and 4-hour post-SC experimental group after perfusion with 0.1M phosphate buffer containing 4% paraformaldehyde and 0.1 M sucrose and overnight fixation in freezing.

The time-response rated scores obtained in neural, sensorial and motor activity tests during evaluation performed by open-field testing had a normal performance in control (sham) non-SC group. Increasing spinal cord compression time-course from five to 60-sec resulted in graded time-dependent decreases, in sensitive (neurosensorial scores 4-h post-SC - 5 sec: 2 ± 0.5; 15 sec: 1.7 ± 0.9; 30 sec: 1 ± 0.8 and 60 sec: 0.7 ± 0.6; group 24-h post-SC - 5 sec: 2 ± 0.5; 15 sec 1.8 ± 0.9; 30 sec: 1 ± 0.9 and 60 sec: 0.7 ± 0.6 and group 48-h post-SC - 5 sec: 2 ± 0.5; 15 sec: 1.3 ± 0.8; 30 sec: 1 ± 0.8 and 60 sec: 0.6 ± 0.4) and motor activity test scores (motor activity 4-h post-SC - 5 sec: 5 ± 0.1; 15 sec: 3.7 ± 0.4; 30 sec: 2.5 ± 0.5 and 60 sec: 1.6 ± 0.8; group 24-h post-SC - 5 sec: 4.7 ± 0.2; 15 sec: 4.4 ± 0.3; 30 sec: 3.5 ± 0.4 and 60 sec: 2.2 ± 0.5 and group 48-h post-SC - 5 sec: 4.5

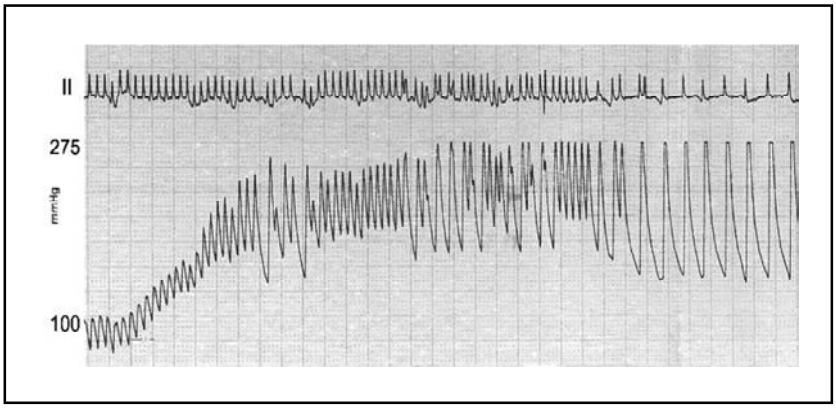

Fig 1. Representative responses of heart rate, systolic and diastolic blood pressure recorder obtained during 60-seconds increased spinal cord compression in rats.

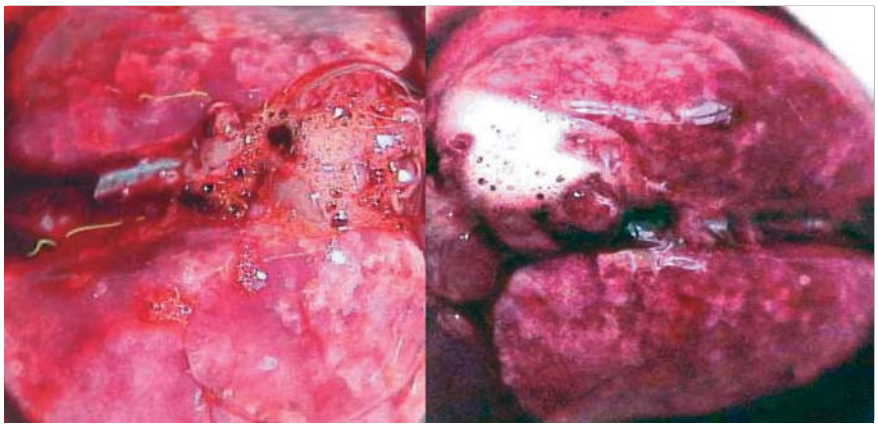

Fig 2. Macroscopic aspects of the pulmonary edema in rats submitted to spinal cord compression study during 60 seconds.

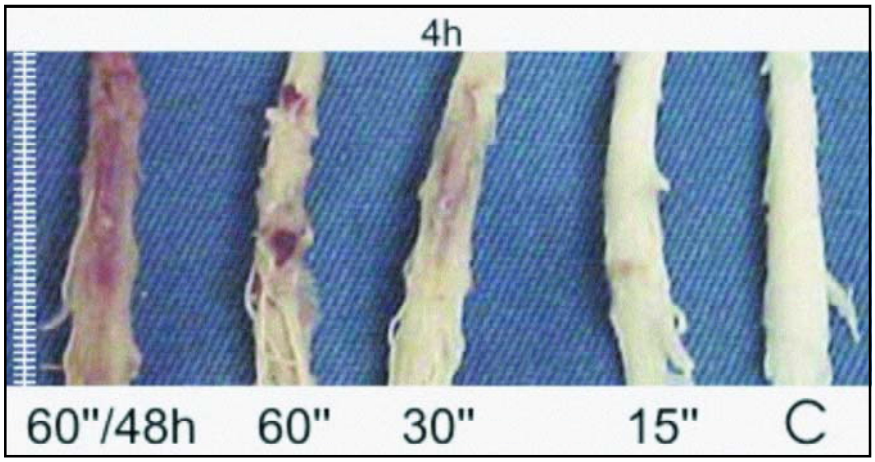

Fig 3. Time-course morphological aspects of the spinal cord in rat control and experimental groups according to the time of compression (15, 30 or 60 seconds) evaluated 4-h after compression.

± 0.3; 15 sec: 3.6 ± 0.4; 30 sec: 2.5 ± 0.5 and 60 sec: 1 ± 0.8). Although there was significant and gradual time-dependent increase in motor (p = 0.001) and neurosensorial (p = 0.02) deficits, these abnormalities were unaffected when evaluated at 4, 24 and 48 hours after SC (motor activity scores, p = 0.5 and neurosensorial scores, p = 0.1).

Histologic examination of the spinal cord showed in the area of compression parenchymal ruptures accompanied by acute hemorrhage. Light microscopic examination of pulmonary tissue showed vascular congestion with perivascular edema and a varying amount of intra-alveolar accumulation of proteinaceous fluid. Comparison of pulmonary index and morphometric data obtained by light microscopy in paraffin sections showed that relevant intra-alveolar edema occured only for index values above 0.55. The pulmonary edema was investigated by the pulmonary index that was 0.395 ± 0.018 in control group, rose to 0.499 ± 0.060 in group 2, and was 0.639 ± 0.14; p=0.0018 in group 3.

DISCUSSION

Since the diagnosis of neurogenic pulmonary edema is often based on exclusion and as many cases may be subclinical, the incidence of neurogenic pulmonary edema may be underestimated. In the mammalian lung, alveolar gas and blood are separeted by an extremely thin membrane, despite the fact that mechanical failure could be catastrophic for gas exchange. Stress failure causes increased permeability with protein leakage or frank hemorrhage, and probably has a role in several types of lung disease. In anesthesized rabbits, at capillary transmural pressures greater-than-or-equal-to 40 mmHg, disruption of the capillary endothelium and alveolar epithelium was seen in some locations[4]. Neurogenic pulmonary edema is associated with a varie-

ty of central nervous system lesions. Some authors explain that a massive centrally mediated sympathetic discharge occurs as a result of the lesion[7-11].

In the present experimental model, the behavioral tests after 60 seconds of spinal cord compression showed a striking influence of this procedure in the neurological performance. Six animals that were submitted to a spinal cord compression for 60 seconds (Fig 3) developed pulmonary edema, all of them in the 4-h group (Fig 2). Additionally, as demonstrated in the Figure 1, the spinal cord compression during 60 seconds also resulted in elevation of the arterial pressure and drop in the heart rate. This evidence corroborates the hypothesis of massive centrally mediated sympathetic discharge.

Nathan and Reis observed that bilateral electrolytic lesions of the anterior hypothalamus in unrestrained rats resulted within 2 hours in the development of arterial hypertension, tachycardia, hyperthermia and increased locomotor activity, often leading to pulmonary edema and death. Similar lesions in paralyzed, artificially ventilated rats produced comparable changes. They 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 lesion inducement prevented the development of arterial hypertension and pulmonary edema, as well as the changes in peripheral resistance, cardiac output, and body temperature[7]. Glazer and Ross observed noradrenergic (NE) bulb-spinal innervation to midthoracic sympathetic preganglionic nuclei in the rat thoracic cord by immunocytochemical localization of dopamine-beta-hydroxylase, a specific NE antigen[8].

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. Experimental work tested this hypothesis by evaluating the relationship between the degree of pulmonary hypertension and postmortem extravascular lung water content (EVLW) in both non-vagotomized and vagotomized rabbits, which had been administred thrombin and fibrinogen intracisternally[12]. The conclusion for this study revealed that vagotomy had no protective effect but instead appeared to increase the amount of edema development for a given degree of pulmonary hypertension[12].

Widdicombe reported that the trachea-bronchial vasculature is controlled by adrenergic, cholinergic and peptidergic nervous mechanisms[13]. This author show that sympathetic nerves release norepinephrine and neuropeptide Y (both of which are constrictor agents) while parasympathetic nerves release acetylcholine and usually vasoative 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[13]. 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)[13].

The neuropeptide Y is believed to be an important mediator in neurogenic pulmonary edema, responsible for the increased pulmonary vascular permeability and differences in receptor modulation. This might be an explanation for the fact that neurogenic pulmonary edema could be more pronounced due to administration of sodium pentobarbital when this anesthesic is used[14] and justify the pulmonary edema verified in the present experiment, where the xylazine could modulate noradrenergic receptors and ketamine, neuropepyide Y receptors, differently from sodium pentobarbital.

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 pretreatment with PPP, a sigma receptor agonist, or scopolamine, a muscarinic cholinergic antagonist, prevented pulmonary failure and death[15]. Based on these results, it is suggested that the VMR has a role in regulation of pulmonary blood flow and that the preliminary pharmacological studies suggest that disruption of glutamatergic and cholinergic mechanisms mediates the lethal pulmonary phenomenon[15]. Imaizumi et al. had always investigated the role of the caudal ventrolateral medulla (CVL) in rats[10].

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 myo-

cardial contractility as well as peripheral vasomotor tone, and that dysfunction of these medullary neurons could underlie some forms of experimental hypertension[16]. 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-edema from fliud-percussion brain injury in the adult-rat[17].

It was suggested that when endotheliumderived relaxing factor (EDRF) release is inhibited during massive sympathetic nervous system activity, pulmonary vascular resistance is markedly increased, which causes the right ventricule to fail. The reduced right ventricular output maintains pulmonary microvascular pressure below levels required for edema development[18]. 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[19].

The intrathecal (i.t.) injection of endothelins to conscious rats was found to cause respiratory arrest. The increase of pulmonary vascular permeability and edema induced by i.t. 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[20].

Hamdy et al. 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 edema in rats[21]. Sympathetic hyperactivity during sudden intracranial hypertension leads to cardiovascular instability, myocardial dysfunction and neurogenic pulmonary edema. One study observed that intrathecal lidocaine prevents cardiovascular collapse and neurogenic pulmonary edema in a rat model of acute intracranial hypertension[22].

Other research brought new data on the spinal mechanisms of autonomic dysreflexia and cardiovascular dysfunctions, such as visceral stimulation of rats with chronic spinal cord injury that activate adrenal sympathetic preganglionic neurons, which could induce release of catecholamines by the adrenal medulla[23]. The effects of nitric oxide (NO) in the central nervous system on incidence and severity in the fibrin-induced pulmonary edema model were evaluated in rats that were left unilaterally vagotomized 1, 2 and 4 weeks before injections of fibrinogen and thrombin into the cisterna magna, after sectioning of the right vagus nerve. In the present study, the brain NO synthase level in the medulla oblongata was elevated in the 2-week group, compared to the control, but decreased in the 4-week group. Incidences of pulmonary edema were 100% in the control group, decreasing to 78% in the 1-week group, 17% in the 2-week group and back to 72% in the 4-week group. The lung water ratio, a parameter of severity, demonstrated a similar pettern of change as the incidence. The lowered incidence and severity obtained in the 2-week group were reversed by intracisternal injection of N-omega-nitro-L-arginine methyl ester (L-NAME). These results sustain the idea that an increase in nitric oxide, possibly in the nucleus tractus solitarius 2 weeks after left vagotomy, may have an inhibitory action on the development of neurogenic pulmonary edema in rats[24].

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.The CVL medulla sends projections to the spinal intermediolateral nucleus, where preganglionic neurons take control of heart and blood vessels (T2 segment) and adrenal medulla (T8 segment)[25]. In the present experiment the compression was done in the middle thoracic spine cord and this fact could probably justify the occurence of hemodynamics disturbances and pulmonary edema.

Electron-microscopic appearances of pulmonary capillaries were studied in rabbit lungs perfused in situ when the capillary transmural pressure (Ptm) was systematically raised. Normal appearances were seen at 12.5 cm H2O Ptm. At 52.5 and 72.5 cm H2O Ptm, striking discontinuities of the capillary endothelium and alveolar epithelium were seen. A few disruptions were seen at 32.5 cm H2O Ptm, whe-

re the mean frequency was 27.8 ± 8.6 and 13.6 ±1.4 (SE) breaks/mm for endothelium, respectively[26].

Morphological characteristics of changes in the spine and lungs of patients with spine injuries who died in hospital were: spinal edemas, morphological changes in the lungs characterized by a phase-wise process, depended on the volume of injury, duration of hospitalization and medical care, manifested by disorders of blood content of the organ, development of tissue edema, and pneumonia[27].

In the present study the histologic evidence of parenchymal ruptures and acute hemorrhage caracterized the spinal cord injury and it was coincident with the pulmonary edema in the group of sodium pentobarbital under 60 seconds balloon-compression. The histologics evidence described and the hemodynamic parameters evaluated corroborate with the idea that the pulmonary edema had an important participation of the anesthetic drug in the genesis of the neurogenic pulmonary edema.

Some experiences in the literature are reviewed and related, for example: acute neurogenic pulmonary edema in a 28-year-old woman who presented rupture of an internal carotid artery aneurysm and subarachnoid hemorrhage[28]; two patients with neurogenic pulmonary edema, one with head injury and another with intracerebral hemorrhage[29]; neurogenic pulmonary edema after injuries of the cervical spine[30]; evidence of lung injury during reconstructive thoracolumbosacral surgery for adult spinal deformities with pulmonary artery pressure monitoring[31]; sudden unexpected and unexplained death in autopsied epilepsy patients, most of whom had pulmonary and/or cerebral edema as the cause of death[32].

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 hemodynamic 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 edema.

REFERENCES

1. Schwarz S, Schwab S, Keller E, Bertram M, Hacke W. Neurogenic impairment of cardiopulmonary function in acute cerebral lesions. Nervenarzt 1997;68:956-962.
2. West JB, Mathieu-Costello O. Structure, strenght, failure, and remodeling of the pulmonary blood-gas barrier. Ann Rev Physiol 1999;61: 543-572.
3. West JB, Mathieu-Costello O. Stress-induced injury of pulmonary capillaries. Proc Assoc Am Phys 1998;110:506-512.
4. West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. J Appl Physiol. 1991;70:1731-1742.
5. 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;15:144-150.
6. Khan T, Havey RM, Sayers ST, Patwardhan A, King WW. Animal models of spinal cord contusion injuries. Lab Anim 1999;49:161-172.
7. 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;37:226-235.
8. 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.
9. Kiker JD, Woodside JR, Jelinek GE. Neurogenic pulmonary edema associated with autonomic dysreflexia. J Urol 1982;128:1038-1039.
10. 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.
11. Barbeito L, Fernandez C, Silveira R, Dajas F. Evidences of a sympathoadrenal dysfunction after lesion of the central noradrenergic pathways in rats. J Neural Transm 1986;67:205-214.
12. Bosso FJ, Lang SA, Maron MB. Role of hemodynamics and vagus nerves in development of fibrin-induced pulmonary-edema. J Appl Physiol 1990;69:2227-2232.
13. Widdicombe JG. Neural control of airway vasculature and edema. Am Rev Resp Dis 1991;143(Suppl):S18-S21.
14. 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;373:165-170.
15. Carruth MK, Fowler AA, Fairman RP, Mayer DJ, Leichnetz GR. Respiratory-failure without pulmonary-edema following injection of glutamate agonist into the ventral medullary paphe of the rat. Brain Res Bull 1992;28:365-378.
16. Drolet G, Chalmers J, Blessing W. Vasodepressor neurons in medulla alter cardiac contractility and cardiac output. Hypertension 1993;21:210-215.
17. 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;78:610-618.
18. Pilati CF, Maron MB, Bosso FJ. Role of EDRF in the cardiopulmonary dysfunction produced by massive sympathetic activation. J Appl Physiol 1995;78:1642-1650.
19. Chen HI. Hemodynamic mechanisms of neurogenic pulmonary edema. Biol Sig 1995;4:186-192.
20. Poulat P, Couture R. Increased pulmonary vascular permeability and oedema induced by intrathecally injected endothelins in rat. Eur J Pharmacol 1998;344:251-259.
21. Hamdy O, Nishiwaki K, Yajima M, et al. Presence and quantification of neuropeptide Y in pulmonary edema fluids in rats. Exp Lung Res 2000;26:137-147.
22. Hall SRR, Wang L, Milne B, Ford S, Hong M. Intrathecal lidocaine prevents cardiovascular collapse and neurogenic pulmonary edema in a rat model of acute intracranial hypertension. Anesth Analg 2002;94:948-953.
23. Leman S, Sequeira H. Activation of adrenal preganglionic neurons during autonomic dysreflexia in the chronic spinal cord injured rat. Auton Neurosci 2002;98:94-98.
24. Feng GG, Nishiwaki K, Kondo H, Shimada Y, Ishikawa N. Inhibition of fibrin-induced neurogenic pulmonary edema by previous unilateral left-vagotomy correlates with increased levels of brain nitric oxide synthase in the nucleus tractus solitarii of rats. Autonomic Neuroscience Basic and Clinical 2002;102:1-7.
25. Viltart O, Mullier O, Bernet F, Poulain P, Ba-M'Hamed S, Sequeira H. Motor cortical control of cardiovascular bulbar neurones projecting to spinal autonomic areas. J Neurosci Res 2003;73:122-135.
26. Tsukimoto K, Mathieu-Costello O, Prediletto R, Elliott AR, West JB. Ultrastructural appearances of pulmonary capillaries at high transmural pressures. J Appl Physiol 1991;71:573-582.
27. Solokhin EV, Belova TS, Naumov MR, et al. Morphological changes in lungs of patients with spinal injuries died in hospital. Sud Med Ekspert 2000;43:17-19.
28. Brito JCD, Diniz MCA, Rosas RR, Da Silva JAG. Acute neurogenic pulmonary edema: case report. Arq Neuropsiquiatr 1995;53:288-293.
29. Dragosavac D, Falcão ALE, Araújo S, Terzi RGG. Neurogenic pulmonary edema: report of two cases. Arq Neuropsiquiatr 1997;55:305-309.
30. Stocker R, Burgi U. Respiratory problems after injuries of the cervical spine. Schweiz Med Wochenschr 1998;128:1462-1466.
31. Urban MK, Urquhart B, Boachie-Adjei O. Evidence of lung injury during reconstructive surgery for adult spinal deformities with pilmonary artery pressure monitoring. Spine 2001;26:387-390.
32. Antoniuk SA, Oliva AV, Bruck I, Malucelli M, Yabumoto S, Castellano JL. Sudden unexpected, unexplained death in epilepsy autopsied patients. Arq Neuropsiquiatr 2001;59:40-45.