Indian J Physiol Pharmacol 1998; 42 (1) : 71–80

DEVELOPMENT OF NEUROGENIC PULMONARY EDEMA AT DIFFERENT GRADES OF INTRACRANIAL PRESSURE IN CATS

YOGENDRA K. GUPTA*, ANITA CHUGH, VINEET KACKER, VIR S. MEHTA* AND PRAKASH N. TANDON*

Neuropharmacology Laboratory,
*Departments of Pharmacology and *Neurosurgery,*
All India Institute of Medical Sciences,
New Delhi – 110 029

(Received on February 15, 1997)

Abstract : Development of neurogenic pulmonary edema (NPE) subsequent to increased intracranial pressure (ICP) was evaluated in an experimental model in cats. Experiments were conducted in chloralose anaesthetised animals, either on spontaneous respiration or on intermittent positive pressure ventilation. Hemodynamic parameters i.e., mean arterial pressure (MAP) and heart rate (HR) were continuously monitored. Pulmonary artery/ right ventricular systolic pressure was recorded in cats on spontaneous respiration. Increase in ICP for 180 minutes caused an increase in extravascular lung water (EVLW) content in both spontaneously breathing and artificially ventilated animals. In spontaneously breathing animals EVLW to blood free dry weight ratio (EVLW/BFDW) was 3.95 ± 0.16 and 4.96 ± 0.16 at ICP 40 and 80 mm Hg respectively while in animals on artificial ventilation, at 40, 60, 80 and 100 mm Hg ICP, it was 3.88 ± 0.11, 4.09 ± 0.10, 4.50 ± 0.13 and 5.03 ± 0.17 respectively. These values were significantly greater ($P<0.05$) as compared to that in sham operated animals (3.43 ± 0.10). This was accompanied by rise in MAP, HR and pulmonary artery pressure. The study establishes the graded development of NPE, the severity of which is proportional to the levels of ICP.

Key words : intracranial pressure, neurogenic pulmonary edema, extravascular lung water, blood free dry weight

INTRODUCTION

Pulmonary edema developing subsequent to central nervous system insults e.g., head injury, stroke, seizures, etc. has been termed as "Neurogenic Pulmonary Edema" (1–5). Although reported incidence of frank pulmonary edema is very low, observations from patients with central nervous system insults reveal high incidence of respiratory complications (6–8), which may or may not be accompanied by appreciable hemodynamic alterations. The development of pulmonary edema has generally been attributed to aspiration, infection, or adult respiratory distress syndrome (9–10). However, the possibility of these complications being the consequence of, at least in some cases, low grade pulmonary edema as primary pathology independent of

*Corresponding Author

changes in blood pressure, or as a condition predisposing to infection cannot be ruled out (11). Increased intracranial pressure is a common factor in most central nervous system insults associated with NPE. Experiments addressing the pathophysiology of NPE have generally raised ICP to very high levels (150–200 mm Hg) and for a relatively brief duration (12–15). The rise in ICP is accompanied by marked systemic and pulmonary hemodynamic changes. But clinically, pulmonary complications have even been observed in patients without evidence of any significant hemodynamic alterations (2, 16–18). Very few studies have, however, focussed on levels of ICP (30–40 mm Hg) that are commonly found in patients following head injury or stroke (19).

This experimental study in anaesthetised cats explores the effect of different grades of mild to moderate levels of increased ICP (40–100 mm Hg) for prolonged duration (180 mins) on the development of NPE and the associated hemodynamic parameters.

METHODS

Healthy mongrel cats of either sex, weighing 2.5 – 4.5 kg were used. Cats were anaesthetised with chloralose 80 mg/kg, i.p. (10% solution in propylene glycol). Experiments were conducted in two groups. In one adequate oxygenation was ensured by artificially ventilating (IPPV) the animals with "Harvard Respirator" attached to the tracheal cannula (tidal volume 10 ml/kg; tidal frequency 15/min). In the other group, the animals were allowed to remain on spontaneous respiration. Head was fixed in a stereotactic frame. A No. 22 needle was placed stereotaxically in right and left lateral cerebral ventricle. ICP was continuously monitored from the cannula in the left lateral cereberal ventricle. The ICP recording was done on Grass Model 7D polygraph using a Statham P 23D transducer.

Right femoral artery was cannulated with a polyethylene tube filled with haparinised saline (50 U/ml) and connected to a Statham P 23D transducer to monitor systemic arterial pressure. Mean arterial pressure was calculated as :

$$\text{MAP} = \frac{\text{Systolic pressure} + \text{Diastolic pressure}}{2} + \text{Diastolic pressure}$$

A 5F catheter filled with heparinised saline (50 U/ml)) was advanced from the right femoral vein into the pulmonary artery or the right ventricle and connected to a Statham P 23D transducer for recording the pulmonary artery/right ventricular pressure. However, the recording of pulmonary artery pressure was done only in animals placed on spontaneous respiration. The correct placement of the catheter was ensured by using the pressure recording as a guide and on postmortem examination. Heart rate of the animals was recorded using standard ECG limb lead II. All recordings were done on a Grass Model 7D polygraph.

The needle placed in right lateral cerebral ventricle was connected to the buffered saline pressure head (pH 7.2). The ICP was increased and maintained at the desired level of 40, 60, 80 and 100 mm Hg in animals on IPPV and 40, and 80 mm Hg in animals on spontaneous respiration, by adjusting the height of the reservoir. Six experiments were conducted in each group (Control and different levels of raised ICP) and were observed for 180 mins. Concurrent

controls as sham operated animals with IPPV and spontaneous respiration were also studied. In these animals right lateral cereberal ventricle was not connected to buffered saline pressure head and instead saline was infused intravenously at the rate of 1 ml/min. The animals were sacrificed with an overdose of chloralose (300 mg/kg, iv). Twenty five ml of blood was withdrawn from the heart. Trachea was clamped, a ligature was tied around right and left major bronchi and lungs were dissected out quickly (within 5 min).

Extravascular lung water was calculated by the method as described by Holcroft and Trunkey (20). The removed lung was allowed to drain passively for 2 min, weighed and homogenised with equal weight of distilled water in the blender. An aliquot of well stirred homogenate was centrifuged at 12,000 rpm at 4°C for 60 min (Dupont Sorvall 16Rc 5 P) to obtain a clear supernatant. The water content of the blood, lung homogenate and supernatant was determined by measuring wet and dry weights of aliquots, of each before and after complete drying at 80 ± 5°C. Complete drying was ascertained by unchanged weights on two successive weighings at 24 hr intervals. Hemoglobin content of the blood withdrawn and the supernatant was estimated by cyanmethemoglobin method. Extravascular lung water expressed as per gm of blood free dry weight was used as an index of pulmonary edema. The formula used was as follows:

Blood wt. =

$$\frac{\text{Hb (supernatant)}}{\text{Hb (blood)}} \times \frac{H_2O \text{ (homogenate)}}{H_2O \text{ (supernatant)}} \times \text{homogenate wt.}$$

Blood H_2O = % $H_2O_{(blood)}$ X BW

Total Lung H_2O = [% H_2O (homogenate) X homogenate wt.] - Added H_2O

Extravascular lung water = TLW – Blood H_2O

Blood free dry wt. = Wet lung wt. - BW - EVLW

EVLW/BFDW : Index of Pulmonary Edema

The values are expressed as mean values ± SE and were compared using unpaired 't' test.

RESULTS

All the animals survived the observation period of 180 min and were sacrificed except the animals on spontaneous respiration in which ICP was raised to 80 mm Hg. The survival time in these animals ranged from 75–110 mins.

Animals placed on spontaneous respiration

Control : In the sham operated control animals in which intracranial pressure was not increased, the ICP ranged from 3 to 12 mm Hg with a mean of 5 ± 2 mm Hg. This group has been referred to as control (5 mm Hg) group.

The baseline mean arterial pressure in 8 sham operated animals on spontaneous respiration was 101 ± 7 mm Hg (mean ± SEM) which remained stablized at this level till 180 mins. The heart rate also remained stable throughout the observation period around the baseline level of 188 ± 10 beats/min. Pulmonary artery pressure could be recorded in 6 out of the total 8 cats and was stable at the baseline level of

15.01 ± 0.36 mm Hg throughout the observation period (Table I).

TABLE I : Effect of increased intracranial pressure on Extra vascular Lung Water in cats placed on spontaneous respiration.

Group	ICP (mm Hg)	n	Extravascular lung water (g water/g blood free dry wt)		Percent increase
			Range	Mean ± SE	
1	05 (Control)	8	2.48 – 3.17	2.94 ± 0.08	
2	40	7	3.13 – 4.53	3.95 ± 0.16**	34.5%
3	80	6	4.60 – 5.81	4.96 ± 0.16***	68.7%

**P<0.01 compared to Group 1

***P<0.001 compared to Group 1

The EVLW values in the sham-operated animals on spontaneous respiration ranged from 2.48 to 3.17 with a mean ± SEM of 2.94 ± 0.08 (Table II).

TABLE II : Effect of different grades of intracranial pressure on mean arterial pressure in cats placed on spontaneous respiration.

Group	ICP (mm Hg)	Mean Arterial Pressure (mm Hg) Time points (Mins)							
		–15	5	15	30	60	90	120	180
1	0 (Control)	101 ±7	101 ±7	100 ±8	100 ±8	101 ±8	100 ±8	102 ±8	102 ±8
		..... n=8							
2	40	106 ±6	104 ±6	101 ±5	99 ±5	104 ±9	109 ±6	106 ±2	103 ±2
		..... n=7					n=6	..... n=4	
							1 died	2 died	
3.	80	105 ±6	129 ±5	151 ±8	151 ±9	164 ±8	149 ±6	123 ±2	–
		..... n=6					n=5	n=2	n=0
							1 died	3 died	2died

ICP 40 mm Hg : Seven cats were studied in this group. The baseline MAP was 106 ± 6 mm Hg which did not change significantly till 90 mins after increasing the ICP. One cat died at 105 mins. In this cat there was a sudden rise in MAP to 176 mm Hg, while two others died between 120 to 135 mins, though there was no change in MAP in these cats. The MAP at 150 mins was 103 ± 2 mm Hg which did not change significantly thereafter (Table I).

The baseline heart rate in these animals was 195 ± 8 beats/min which decreased to 183 ± 9 beats/min and 74 ± 12 beats/min at 5 min and 30 mins after increasing the ICP.

TABLE III : Effect of different grades of intracranial pressure on heart rate in cats placed on spontaneous respiration.

Group	ICP (mm Hg)	Heart Rate (beats/min) Time Points (Mins)							
		–15	5	15	30	60	90	120	180
1	0 (Control)	188 ±10	190 ±10	190 ±10	190 ±10	193 ±11	193 ±11	193 ±11	193 ±10
		..... n=8							
2	40	195 ±8	183 ±9	180 ±10	174 ±12	174 ±12	175 ±11	170 ±13	173 ±6
		..... n=7				n=6	..... n=4		
							1 died	2 died	
3.	80	193 ±5	209 ±5	218 ±6	220 ±8	227 ±11	201 ±20	225 ±4	–
		..... n=6					n=5	n=2	n=0
							1 died	3 died	2died

No change in pulmonary artery/right ventricular systolic pressure was seen in any of the animals throughout the observation period of 180 mins, as compared to the baseline level of 21.6 ± 1.9 mm Hg.

The EVLW values in this group of seven cats ranged from 3.13 to 4.53 with a mean of 3.95 ± 0.16. This was significantly greater

TABLE IV : Effect of different grades of intracranial pressure on pulmonary artery/right ventricular systolic pressure in cats placed on spontaneous respiration.

Group	ICP (mm Hg)	Pulmonary Artery/Right Ventricular Systolic Pressure (mm Hg) Time Points (Mins)							
		-15	5	15	30	60	90	120	180
1	0 (Control)	23.2 ±1.7	23.2 ±1.8	23.2 ±1.8	23.1 ±1.8	23.4 ±2.0	23.4 ±2.0	23.2 ±2.0	23.1 ±2.0
		..... n=8							
2	40	21.6 ±1.9	21.4 ±1.9	22.2 ±1.6	22.8 ±1.7	23.8 ±1.9	23.4 ±1.6	25.6 ±1.8	26.0 ±2.3
		..... n=7					n=6 1 died	..... n=4	
3	80	21.1 ±1.8	32.2 ±2.0	32.6 ±2.9	32.6 ±3.0	35.0 ±3.6	36.6 ±5.0	36.2 ±6.2	–
		..... n=6					n=5 1 died	n=2 3 died	n=0 2 died

TABLE V : Effect of different grades of intracranial pressure on Extravascular Lung Water in cats placed on intermittent positive pressure ventilation (IPPV).

Group	ICP (mm Hg)	n	Extravascular lung water (g water/g blood free dry wt)		Percent increase
			Range	Mean ± SE	
1	05	6	3.13 – 3.90	3.43±0.10	
2	40	6	3.58 – 4.31	3.88±0.11*	13%
3	60	6	3.63 – 4.38	4.09±0.10**	19%
4	80	6	4.12 – 5.05	4.50±0.13***	31%
5	100	6	4.51 – 5.69	5.03±0.17***	47%

* P<0.05 compared to Group 1
** P<0.01 compared to Group 1
*** P<0.001 compared to Group 1

as compared to sham operated control animals (P<0.01).

ICP 80 mm Hg : In 6 cats ICP was increased to 80 mm Hg, in which the baseline MAP was 105 ± 6 mm Hg. On increasing the ICP, the systolic, diastolic and mean arterial pressure started increasing within 5 mins and continued to rise till 60–75 mins, when one cat died. Subsequently, a trend of gradual reduction of MAP was observed. The MAP at 15 mins was 151 ± 8 mm Hg and at 60 mins was 146 ± 10 mm Hg. All the animals in this group died within 180 mins.

TABLE VI : Effect of different grades of intracranial pressure on mean arterial pressure in cats placed on intermittent positive pressure ventilation.

Group	ICP (mm Hg)	Mean Arterial Pressure (mm Hg) Time Points (Mins)							
		–15	5	15	30	60	90	120	180
1	0 (Control) (n=6)	98 ±8	98 ±8	98 ±8	98 ±8	99 ±8	98 ±8	98 ±8	100 ±9
2	40 (n=6)	98 ±9	100 ±9	99 ±8	99 ±10	99 ±10	101 ±10	101 ±10	103 ±9
3	60	95 ±8	116 ±7	110 ±11	104 ±11	98 ±10	98 ±10	101 ±9	99 ±10
4	80	93 ±8	126 ±4	124 ±4	123 ±4	123 ±5	125 ±4	124 ±5	122 ±5
5	100	94 ±8	129 ±8	132 ±8	132 ±8	134 ±8	125 ±4	127 ±4	127 ±4

The baseline HR in this group was 193 ± 5 beats/min, which increased to 209 ± 5 beats/min at 5 mins and to 227 ± 11 beats/min at 60 mins after increasing the ICP to 80 mm Hg. The increase in HR was maintained even during the hypotensive phase.

In contrast to ICP 40 mm Hg, the pulmonary artery pressure increased to 32.2 ± 2 mm Hg at 5 mins after increasing the ICP to 80 mm Hg. At 60 mins, this pressure was 33.9 ± 3.6 mm Hg, and remained at or near this level for the remaining period in the surviving cats.

In cats in which ICP was increased to 80 mm Hg, the EVLW values ranged from 4.60 to 5.81, with a mean of 4.96 ± 0.16. The values were significantly greater than the sham-operated controls (P<0.001).

TABLE VII : Effect of different grades of intracranial pressure on heart rate in cats placed on intermittent positive pressure ventilation.

Group	ICP (mm Hg)	Heart Rate (beats/min) Time Points (Mins)							
		–15	5	15	30	60	90	120	180
1	0 (Control) (n=6)	188 ±7	190 ±7	190 ±7	190 ±7	193 ±7	195 ±8	192 ±8	193 ±7
2	40 (n=6)	197 ±7	188 ±11	188 ±8	181 ±11	170 ±11	170 ±11	168 ±9	168 ±11
3	60	192 ±6	211 ±13	201 ±7	199 ±8	199 ±8	190 ±8	189 ±7	188 ±6
4	80	198 ±5	206 ±7	206 ±6	200 ±1	203 ±10	207 ±11	203 ±11	203 ±11
5	100	189 ±6	206 ±8	214 ±11	219 ±10	212 ±9	205 ±11	210 ±12	205 ±10

Animals placed on intermittent positive pressure ventilation (IPPV) :

Control : The baseline MAP in the 6 animals in this group was 98±8 mm Hg which remained constant at this level throughout the 180 min observation period. Similarly, there was no change in HR compared to the baseline level of 188±10 beats/min.

EVLW/BFDW values in this group ranged from 3.13 to 3.90 with a mean±SEM of 3.43±0.10. These values were significantly greater than that in animals allowed to remain on spontaneous respiration (P<0.05).

ICP 40 mm Hg : The baseline MAP in the 6 cats in this group was 98±9 mm Hg which did not change significantly throughout the observation period of 180 mins. The baseline HR was 197±7 beats/min which started declining on raising the ICP to 40 mm Hg. At 60 mins the HR was 170±11

beats/min which was significantly less as compared to the baseline level (P<0.05).

The EVLW/BFDW values ranged from 3.58–4.31 with mean±SE of 3.88±0.11 and were significantly greater (P<0.05) as compared to sham–operated animals.

ICP 60 mm Hg : In group 3 animals the ICP was increased and maintained at 60±2 mm Hg. The baseline MAP in these animals was 95±8 mm Hg which increased significantly to 116±7 mm Hg, 5 mins after increasing the ICP. It subsequently declined at 15 mins to 110±11 mm Hg, which was not significantly different from baseline levels, and remained so throughout the subsequent observation period. Heart rate increased at 5 mins to 211±13 beats/min, compared to the baseline level of 192±6 beats/min (P<0.01). Subsequently it declined to 201±7 beats/min, and was not significantly different from control levels thereafter.

The EVLW/BFDW values ranged from 3.63 to 4.38 with mean±SE of 4.09±0.10 and were significantly greater as compared to the control animals.

ICP 80 mm Hg : In this group of animals the ICP was increased and maintained at 80±2 mm Hg. The baseline MAP was 93±8 mm Hg, which started increasing within 5 secs of increasing ICP. It was 126±4 mm Hg at 5 min, which was significantly greater than the baseline level (P<0.001). In the subsequent observation period, it was maintained at this level. There was no significant change in HR as compared to the baseline level (198±5 beats/min) throughout the 180 min observation period.

The EVLW/BFDW values ranged from 4.12 to 5.05 with mean±SE of 4.50±0.13 and were significantly greater (P<0.001) as compared to the control animals.

ICP 100 mm Hg : The baseline MAP in the six animals in this group was 94±8 mm Hg. It increased significantly to 129±8 mm Hg (P<0.001) at 5 min after raising the ICP, and progressed further to 139±8 mm Hg (P<0.001) at 15 min.

The baseline HR was 189±6 beats/min which increased on raising the ICP. It was 206±8 beats/min at 5 mins and reached its maximum level at 45 mins (222±10 beats/min; P<0.001). Subsequently it showed a decline but was still significantly greater that the baseline level.

In animals in which ICP was increased to 100±3 mm Hg, the EVLW/BFDW ratio ranged from 4.51 to 5.69 with mean±SE of 5.05±0.17 which was significantly greater as compared to the sham operated control animals.

DISCUSSION

Earlier reports by Hoff et al (15, 21) and Nishimura and Hoff (22) had established consistent development of neurogenic pulmonary edema in cats when ICP was increased to 150–200 mm Hg for a period of 30 mins. In the present study in cats, development of "Neurogenic Pulmonary Edema" as indicated by increase in EVLW/BFDW ratio was observed at different ICP levels from 40 to 100 mm Hg in 180 min. The edema formation was proportional to the increase in ICP. This study suggests

that subsequent to relatively low levels of ICP, development of NPE progresses slowly to manifest only after a lapse of some time. The reported absence of development of NPE at ICP of 100 mm Hg by Hoff et al (15) could be sttributed to shorter duration of raised ICP (30 mins). This contention is supported by the finding of Newman et al (19) who observed development of interstitial edema subsequent to increasing ICP to 30 mm Hg for 5 hrs in cats. In their study the cats were allowed to remain on spontaneous respiration and thus became hypoxic and hypercapneic. In the present study, the increase in extravasular fluid was also observed at such levels of ICP in the animals that were not allowed to become hypoxic and hypercapneic, by providing mechanical ventilation. It is therefore, our contention that increased ICP and not the secondary hypoxia or hypercapnia is the important mechanism underlying extravasular fluid accumulation.

Mild increase of ICP e.g., 40 mm Hg may cause a slower distortion of brain stem (23) and consequently delay stimulating the centres that produce sympathetic discharge/ other mediators/stimulus involved in mediation of NPE. The relationship between intracranial pressure and pulmonary vascular responses have been reported (24, 25). The release of chemical or neural mediators whose concentration is graded according to severity of ICP has been postulated, which can account for extravascular fluid accumulation proportional to the level of ICP (25).

Some researchers have failed to observe significant increase in extravascular lung water subsequent to increasing ICP following similar experimental procedures (i.e., increased ICP to 60–70 mmHg for 2–3 hrs) in sheep (25, 26), which could be attributed to the non-susceptibility to pulmonary edema due to species variation.

Species variation and slow progression of pulmonary edema are thus two factors that may explain why pulmonary edema has scarcely been reported previously in experimental studies subsequent to mild to moderate levels of increased ICP.

Systemic arterial hypertension has consistenly been observed in neurogenic pulmonary edema experiments with few exceptions (12, 24, 27-30). In the present study, though significant pulmonary edema developed at all levels of ICP, systemic arterial hypertension was observed only at 80 and 100 mm Hg. At 40 mm Hg, there was no significant change in MAP, though a consistent increase in EVLW content was seen. Newman et al (14) had also observed development of interstitial edema in the absence of significant systemic arterial hypertension in their experiments in cats. Thus, it seems that systemic arterial hypertension is not a prerequisite for the development of NPE.

With the increasing use of continuous ICP monitoring in the management of patients after brain injury, now the correlation between pulmonary edema and increased ICP can be better appreciated.

In the clinical situation, many patients but not all develop pulmonary edema when ICP rises above 40 mm Hg after head injury

and stroke. Further studies in this experimental model are warranted to investigate the factors predisposing an individual to development of neurogenic pulmonary edema.

ACKNOWLEDGEMENTS

This project was funded by a Research Grant from the Department of Science and Technology, Government of India, New Delhi.

REFERENCES

1. Casey WF. Neurogenic pulmonary edema. *Anesthesia* 1983; 38: 731-734.
2. Wray NP, Nictora MB. Pathogenesis of neurogenic pulmonary edema. *Am Rev Respir Dis* 1978; 118:783-786.
3 Koppel BS, Pearl M, Pearl E. Epileptic seizures as a cause of unilateral pulmonary edema. *Epilepsia* 1987; 28: 41-44.
4. Beckman DL, Ginty DD, Gaither AC. Neurogenic pulmonary edema in a pulmonary normotensive model, *Proc Soc Exp Biol Med* 1987; 186: 170–173.
5. Ell SR. Neurogenic pulmonary edema – A review of literature and a perspective. *Invest Radiol* 1991; 26: 499–506.
6. Beckman DL. Pulmonary responses to experimental brain injury. In : Becker DP, Povilishock JR, eds., Central Nervous System Trauma Report. National Institute of Health, 1984: 417–424.
7. Rossi NP, Graf CJ. Physiological and pathological effects of neurologic disturbances and increased intracranial pressure on the lung – A review. *Surg Neurol* 1976; 5: 366–372.
8. Colice GL, Matthay MA, Bass E. Neurogenic pulmonary edema. *Am Rev Respir Dis* 1984; 130: 941–949.
9. Moss G, Stein AA. Cerebral etiology of acute respiratory distress syndrome : diphenylhydantoin prophylaxis. *J Trauma* 1975; 15: 39–41.
10. Petty TL, Reiss OK, Paul GW, Silvers GW, Elkins ND. Characteristics of pulmonary surfactant in adult respiratory distress syndrome associated with truama and shock. *Am Rev Respir Dis* 1977; 115: 531–536.
11. Mehta VS, Bhatia R, Tandon PN, Banerjee AK. Prospective study of pulmonary infection among 100 consecutive head injured patients. *Neurology India* 1982; 30: 131–138.
12. Ducker TB, Simmons RL. Increased intracranial pressure and pulmonary edema. *J Neurosurg* 1968; 28: 118–123.
13. Brashear RE, Pamintuan RL. Increased pulmonary diffusing capacity and elevated cerebrospinal fluid pressure. *J Appl Physiol* 1971; 30: 844–846.
14. Harrison W, Liebow AA. The effects of increased intracranial pressure on the pulmonary circulation in relation to pulmonary edema. *Circulation* 1952; 5: 824–832.
15. Hoff JT, Nishimura M. Experimental neurogenic pulmonary edema in cats. *J Neurosurg* 1978; 48: 383–389.
16. Carlson RW, Schaeffer RC, Michaels SG, Weil MM. Pulmonary edema following intracranial hemorrhage. *Chest* 1979; 75: 731–734.
17. Fein IA, Rackow EC. Neurogenic pulmonary edema. *Chest* 1982; 81: 318–320.
18. Tuoho H, Karasawa J, Shishido H, Yamada K, Yamazaki Y. Neurogenic pulmonary edema in acute stages of hemorrhagic cerebrovascular disease. *Neurosurgery* 1989; 25: 672–678.
19. Newman MM, Kligerman M, Wilcox M. Pulmonary hypertension, pulmonary edema and decreased pulmonary compliance produced by increased ICP in cats. *J Neurosurg* 1984; 60: 1207–1213.
20. Holcroft JW, Trunkey DD. Extravascular lung water following hemorrhagic shock in baboon. *Ann Surg* 1974; 180: 408–417.
21. Hoff JT, Nishimura MC, Roizen MF. Catecholamines and intracranial pressure. *J Neurosurg* 1979; 50: 792.
22. Nishimura M, Hoff JT. Sequential hemodynamic changes in experimental neurogenic pulmonary edema. In Shulman K, Marmarou A, Miller JD et al, eds. Intracranial Pressure IV. New York, Springer-Verlag, 1986: 33–336.

23. Thompson RK, Malina S. Dynamic axial brain stem distortion as a mechanism explaining the cardiorespiratory changes in increased intracranial pressure. *J Neurosurg* 1959; 16: 664–675.

24. Brashear RE, Ross JC. Hemodynamic effects of elevated cerebrospinal fluid pressure : alterations with adrenergic blockade. *J Clin Invest* 1970; 49: 1324–1333.

25. Peterson BT, Rose JC, Brigham K. Effect of naloxone on the pulmonary vascular responses to graded levels of intracranial hypertension in anaesthetised sheep. *Am Rev Respir Dis* 1977; 115: 531–536.

26. Vander Zee H, Malik AB, Lee BC, Hakim TS. Lung fluid and protein exchange during intracranial hypertension and role of sympathetic mechanisms. *J Appl Physiol* 1980; 48: 273–280.

27. Campbell GS, Haddy FJ, Adams WL, Virscher MB. Circulatory changes and pulmonary lesions in dogs following increased intracranial pressure and the effect of atropine upon such changes. *Am J Physiol* 1949; 158: 96–102.

28. Gamble JE, Patton HD. Pulmonary oedema and hemorrhage induced by hypothalamic lesions in rats. *Science* 1951; 113: 626–628.

29. Chen HI, Sun SC, Chai CY. Pulmonary edema and hemorrhage resulting from cerebral compression. *Am J Physiol* 1973; 224: 223–229.

30. Hoff JT, Nishimura M, Gracia-Uria J, Miranda S. Experimental neurogenic pulmonary edema. I. Role of systemic hypertension. *J Neurosurg* 1981; 54: 627–631.