

# *Effect of Hyperventilation, Hypothermia, and Urea on Circulation and Cerebrospinal Fluid Pressure in the Dog*

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THE combination of hypothermia, pulmonary hyperventilation and the intravenous administration of urea is used clinically not only in neurosurgical operations but also for treatment of cerebral hypoxia. On one occasion the use of this technique was associated with unexpected cardiovascular collapse and death of a patient. This case and the experimental study which it initiated are reported in this paper.

## **Case Report**

A 17 month old female child was admitted to this hospital eleven days prior to operation because of congestive heart failure of extracardiac origin. Radiographic examination of the chest revealed cardiomegaly and increased pulmonary vascularity. An electrocardiogram showed definite atrial hypertrophy and right ventricular hypertrophy. Results of blood and urine examinations were within normal limits. Her condition improved following digitalization and the use of diuretics. Five days before the definitive operation, general endotracheal anesthesia with nitrous oxide-oxygen-halothane was administered for retrograde brachial angiography; no difficulties were encountered during the course of this anesthesia. A large arteriovenous malformation of the posterior cerebral artery and the straight sinus was demonstrated and operative correction of this condition was proposed.

The patient, weighing 9.2 kg., received scopolamine 0.15 mg. intramuscularly one hour prior to anesthesia. Induction of anesthesia was carried out using cyclopropane in a semi-closed pediatric circle absorption sys-

tem and intubation performed following succinylcholine 10 mg. intramuscularly. Hypothermia to an esophageal temperature of 29.5° C. was induced by the immersion technique. At this temperature anesthesia was maintained with nitrous oxide-oxygen (500 ml.:500 ml.) and small intermittent supplements of meperidine (30 mg. total dose) administered intravenously. Respirations were controlled throughout. Bilateral isolation of the vessels in the neck was performed so that temporary cerebral occlusion could be performed if necessary. Vital signs remained stable during this procedure save for three transient episodes of bradycardia which were thought to be caused by traction on the carotid sinus and which responded quickly to cessation of manipulation. Fluid and blood replacement were judged to be adequate up to this point. Toward the conclusion of the neck dissection, the administration of urea (Lyophilized Urea and Travert Solution), 1 g./kg., was commenced; administration took 45 minutes. The patient remained supine with the head turned to expose the right parieto-occipital region. Just after draping and coincidental with the last five minutes of urea administration, the pulse fell from 100 to 80 beats per minute. Over the next five minutes, cardiovascular collapse occurred, characterized by progressive bradycardia and hypotension. Cardiac arrest occurred and at thoracotomy the heart was seen to be in standstill. Because of inadequate response to resuscitative measures, it was thought that effective blood flow could be increased by exclusion of this large arteriovenous fistula from the general circulation. This was carried out quickly. However, all attempts at resuscitation were unsuccessful. At post-mortem examination, hypertrophy of the right atrium and right ventricle were present. The valvu-

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TABLE 1. Cerebrospinal Fluid Pressure (mm.)

	Normothermia			Hypothermia			
	Control	‡ Urea	Total Urea	Control	Hypothermia	‡ Urea	Total Urea
	A	B	C	D	E	F	G
Mean	98	95	92	62	51	43	33
Std. Dev.	80.0	35.6	44.7	23.8	25.2	24.8	24.9
SE <sub>m</sub>	8.9	4.0	5.0	8.0	8.4	8.3	8.3

A-B, A-C, B-C, not significant.

D-E, D-F, not significant. D-G, significant.

lar system of the heart was normal, the foramen ovale closed and the ductus arteriosus not patent. Pulmonary arteriosclerosis, characterized by intimal thickening and medial hypertrophy, was marked. Apart from the cranial vascular abnormality, no other central nervous system pathology, such as herniation of the brain stem, was found.

Shortly after this disaster, Bering and Avman,<sup>1</sup> in studies on the dog, suggested that the amount of urea ordinarily administered during normothermia should be reduced considerably because of the occurrence of cardiac arrest during hypothermia. They recommended a dosage of one-third to one-fourth that used at normothermia. Further studies of this problem seemed indicated. The present study was designed to evaluate the effect of one-third and full doses of urea given to hyperventilated dogs both at normothermia and under hypothermic conditions on CSF pressure and to correlate these with cardiac effects using the electrocardiogram, blood pressure and cardiac output as indices. These measurements were chosen because the death of the patient appeared to have been of circulatory origin even though possibly related to some aspect of the cor pulmonale demonstrable at post-mortem examination.

### Method

Twenty experiments were conducted on ten mongrel dogs ranging in weight from 10 to 18 kg. In half of the dogs, a study was carried out at normal body temperature. Two weeks later, the same dogs were studied a second time using hypothermia. This sequence was reversed for the other five dogs.

Anesthesia was induced with intravenous Veterinary Nembutal 25 mg./kg. A cuffed endotracheal tube was inserted, curare 0.45 unit per kilogram (20 units = 3 mg.) given intravenously and controlled ventilation initiated utilizing a Bird assistor-controller ventilator. Hyperventilation was achieved by deliverance of a tidal volume of approximately 500 ml. with a rate of 18 per minute. Anesthesia was at first maintained with 3.5 liters of nitrous oxide and 1.5 liters of oxygen, after 20 minutes reduced to 500 ml. of each gas. The electrocardiogram was recorded continuously. The femoral artery and vein were cannulated and slow intravenous infusions of 5 per cent dextrose in water begun in order to maintain patency. Cisterna magna puncture was performed with a short 18-gauge needle and continuous cerebrospinal fluid pressure monitored via a spinal manometer. During this procedure care was taken to avoid loss of cerebrospinal fluid. Baseline cerebrospinal fluid pressure was recorded before each procedure.

In the hypothermic studies, the dogs were clipped, and hypothermia induced by surface cooling until a rectal temperature of between 28–30° C. was obtained. At this temperature, cardiac output was determined in duplicate by the indicator-dilution method using indocyanine dye. Following rapid infusion of the dye into the inferior vena cava and using a constant withdrawal pump (Harvard), the dye concentration was measured with a Waters XP-250 A densitometer and recorded on a Honeywell oscillograph. The densitometer was calibrated after each study, using the animal's blood and dye from the original bot-

TABLE 2. Cardiac Output (liters/minute)

	Normothermia			Hypothermia			
	Control	‡ Urea	Total Urea	Hypothermia	‡ Urea	Total Urea	Atropine
	A	B	C	D	E	F	G
Mean	2.16	2.07	2.00	1.28	0.96	0.99	1.30
Std. Dev.	0.74	0.74	0.81	0.37	0.35	0.46	0.41
SE <sub>m</sub>	0.25	0.25	0.27	0.12	0.12	0.15	0.21

A-B, B-C, A-C, not significant. A-D, significant.  
D-E, E-F, D-F, F-G, not significant.

tle. Duplicate determinations agreed within 5 per cent. Arterial blood pressure, venous pressure, cerebrospinal fluid pressure and hematocrit were recorded. Because of the possibility of hemoconcentration occurring as a result of urea diuresis, these hematocrit levels were used to adjust the cardiac output determination to the control level. Urevert 0.33 g./kg., *i.e.*, one-third of the total dose, was administered over a 20 minute period and 10 minutes were allowed for stabilization of the cerebrospinal fluid pressure. Cardiac output, hematocrit, blood pressure, and cerebrospinal fluid pressure were again recorded. The remaining urea, 0.66 g./kg., *i.e.*, two-thirds of the total dose, was then given over 40 minutes and the recordings repeated. The same procedure was followed with the dogs at normothermia.

Some of the dogs studied under hypothermia developed bradycardia. Therefore in five dogs under hypothermia, following the urea administration, atropine 1 mg. was given intravenously. When the heart rate had increased, cardiac output and pressures were again measured.

### Results

Alternation of the order of procedure in the two groups did not affect the results.

**Cerebrospinal Fluid Pressure (Table 1).** Cerebrospinal fluid pressures were not elevated in hyperventilated anesthetized dogs. Urea, 1 g./kg., produced no fall in the cerebrospinal fluid pressure when body temperature was normal. When the animals were hypothermic, the fall in CSF pressure was significant only when 1 g./kg. of urea had been infused.

**Cardiac Output (Table 2).** Urea administration did not alter the cardiac output of the normothermic dogs. Hypothermia reduced the cardiac output 40 per cent. Subsequent infusion of urea produced no further decrease in output. While atropine produced an increase in output whenever the heart rate increased, the change was not significant.

**Heart Rate (Table 3).** Heart rate was markedly lower in the hypothermic dogs than in those with normal body temperature. In neither case, however, did urea alter the heart rate. Following atropine, there was a modest increase in heart rate in all five animals. In general, changes in heart rate were accompanied by parallel changes in cardiac output, with little change in stroke volume, as long as the heart rate was normal or low. With tachycardia, the stroke volume decreased.

**Arterial Pressure (Table 4).** Neither hypothermia nor urea produced a significant change in mean arterial pressure. All pressures were normal, and no animal developed hypotension at any time.

**Venous Pressure.** Venous pressures were normal and displayed no significant changes.

TABLE 3. Heart Rate

	Control	Hypothermia	1/3 Urea	Total Urea	Atropine
	A	B	C	D	E
Mean	121	72	62	59	79
Std. Dev.	28.4	14.0	12.7	21.7	15.3
SE <sub>m</sub>	10.0	4.7	4.2	7.2	7.6

A-B,  $P < 0.001$ , very highly significant.  
B-C, C-D, D-E, not significant.

TABLE 4. Mean Arterial Pressure (mm. Hg)

	Control	‡ Urea	Total Urea	Control	Hypothermia	‡ Urea	Total Urea	Atropine
	A	B	C	D	E	F	G	H
Mean	105	103	114	131	127	133	127	119
Std. Dev.	21.3	28.8	29.6	9.7	17.4	24.0	24.1	24.7
SE <sub>m</sub>	7.0	9.6	9.9	3.2	5.8	8.0	8.0	12.3

A-B, B-C, A-C, not significant.

D-E, D-F, D-G, E-F, F-G, G-H, not significant.

**Hematocrit.** Duplicate hematocrit determinations showed little change and there was no definite trend toward either hemodilution or concentration.

**Electrocardiogram.** No ECG abnormalities were noted throughout the procedures.

### Discussion

Cerebral spinal fluid pressure is increased by an increase in intracranial blood volume. A rise in the blood level of carbon dioxide will cause cerebral vasodilation, and by this mechanism elevate cerebrospinal fluid pressure. In the present studies, the accumulation of carbon dioxide was prevented by deliberate hyperventilation. Consequently, the effects of urea were investigated in animals whose control cerebrospinal fluid pressures were within the normal range and not elevated. At normal body temperature, urea (1 g./kg.) did not lower the normal cerebrospinal fluid pressure.

Changes in cerebral blood flow, independent of vascular pressure changes, will also alter cerebrospinal fluid pressure.<sup>3</sup> Total cardiac output, but not the regional flow to the brain, was measured in these experiments. However, the observed 40 per cent reduction in cardiac output with hypothermia may well have been associated with some decrease in cerebral blood flow, since cerebral metabolism is also reduced. This effect would contribute to the lowering of the cerebrospinal fluid pressure observed when urea was administered to the hypothermic animals, even though the control CSF pressures were not elevated.

The rationale behind urea administration is the production of serum hyperosmolarity<sup>4</sup> with a consequent reduction in brain volume. To what extent this process would counteract the cerebral vasodilation caused by increased

blood levels of carbon dioxide was not investigated. However, this may well be effective, for Rosomoff<sup>5</sup> found that urea in large doses, 6 g./kg., would lower the cerebrospinal fluid in dogs breathing spontaneously. Lesser doses, 1.5 g./kg.,<sup>1</sup> produced a significant reduction in the cerebrospinal fluid pressure of the hypothermic dog without assisted respiration. Hypoventilation may well have elevated the initial cerebrospinal fluid in these reports, and thereby contributed to the positive effect of urea.

Bering and Avman<sup>1</sup> noted that the rapid injection of urea caused severe changes in electrolytes characterized by a sharp increase in the serum potassium and fall in serum sodium sufficient in degree to cause marked changes in the electrocardiogram. In the hypothermic state in the dog this was enough to cause ventricular fibrillation. They suggested that this was a strong contraindication to rapid injections of large doses of urea at any temperature.

This investigation was prompted by death from circulatory collapse in a patient undergoing surgery using hypothermia, hyperventilation, and intravenous urea. This case was complicated by the presence of cardiac and pulmonary vascular abnormalities. Under apparently comparable anesthetic conditions in ten normal dogs, there was no instance of hypotension and no decrease in cardiac output when urea was administered. All animals recovered completely, with no evidence of latent damage. We must conclude that when carbon dioxide accumulation was prevented by deliberate hyperventilation, urea in a dose of 1 g./kg. body weight produced no circulatory embarrassment to the anesthetized dog, whether normothermic or hypothermic. Fur-

thermore, in the hyperventilated dog a significant fall of cerebrospinal fluid pressure occurred following the administration of at least 1 g./kg. body weight of urea only under hypothermic conditions.

Further work is indicated to define the threshold dose of urea which will lower the normal cerebrospinal fluid pressure, or the cerebrospinal fluid pressure elevated by carbon dioxide, at normal and reduced body temperatures.

### Summary and Conclusions

Cerebrospinal fluid pressure, cardiac output, arterial and venous pressure, and pulse rate were determined in ten anesthetized, hyperventilated, normothermic dogs who were given urea 1 g./kg. of body weight in two divided doses over one hour. These procedures were repeated after a two-week interval in the same dogs under hypothermia at 30° C.

Cardiac output was reduced by hypothermia. However, urea administration did not alter the cardiac output at either body temperature. Arterial and venous pressures remained unchanged.

Normal cerebrospinal fluid pressure was not lowered by urea, 1 g./kg., when the body temperature was normal. However, under hypothermia, cerebrospinal fluid pressure was

significantly reduced by urea 1 g./kg., but not with a dose of 0.33 g./kg.

When carbon dioxide accumulation is prevented, urea in a dose of 1 g./kg. of body weight produced no circulatory embarrassment in the anesthetized dog whether normothermic or hypothermic.

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**MENDELSON'S SYNDROME** Aspiration of acid gastric juice can result in a chemical pneumonitis, producing bloody, frothy sputum, cyanosis, air hunger, tachycardia, and fever. The syndrome was treated in one patient with urea and invert sugar instead of the previously-recommended hydrocortisone. Dramatic clearing took place with complete recovery. (*Johnson, H.: Pulmonary Aspiration of Gastric Acid: Mendelson's Syndrome. Successful Treatment with Lyophilized Urea and Ten Per Cent Invert Sugar, J.A.M.A. 179: 900 (March 17) 1962.*)