# *Effect of Hyperventilation, Hypothermia and Urea on Circulation and Cerebrospinal Fluid Pressure in the Dog (2)*

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A study of the effects of hyperventilation, hypothermia and urea administration on circulation and cerebrospinal fluid pressure in the dog was made using urea in doses of 2 g./kg. and 6 g./kg. Studies were made in 10 dogs at normal body temperatures and after lowering the temperature to 28°–30° C. The dose of urea that brought about a significant reduction in cerebrospinal pressure in normothermic dogs lay between 1 g. and 2 g./kg. In a previous study the dose which brought about an equal response in cooled animals lay between 1/3 g. and 1 g./kg. Adverse effects on the cardiovascular indices of ECG, blood pressure or cardiac output were not seen at either normal or lowered body temperature in either study.

Young and his associates [1] in 1963 described the effects of pulmonary hyperventilation, hypothermia and urea on circulation and cerebrospinal fluid pressure in the dog. The study was prompted by the unexpected cardiovascular collapse and death of a 17 month old child during operation in which this combination of techniques had been used. The demise occurred before definitive surgery for an intracranial A–V malformation had been performed. Shortly after this occurred, Bering and Avman,[2] as a result of studies on the dog, suggested that probably one-third the usual dose of urea should be adequate during hypothermia. Our subsequent study [1] showed that urea in ⅓ g./kg. or 1 g./kg. dose produced no circulatory embarrassment in hyperventilated anesthetized dogs either at normothermic or hypothermic conditions.

Received from the Division of Anesthesiology and Cardiovascular Laboratory, University of Colorado Medical Center, Denver, Colorado. Accepted for publication September 16, 1964. Dr. Beckwitt is National Institutes of Health Research Fellow in Cardiology.

Rosomoff [3] reported that 6 g./kg. of urea in dogs was "the amount required to achieve equivalent declines of cerebrospinal fluid pressure in the dog when compared to man." The present study examined the possibility as to whether a dose of urea which brings about these equivalent changes in cerebrospinal fluid pressure in the dog could in someway cause adverse cardiovascular effects not seen with smaller doses. Thus, we correlated the cardiovascular indices of ECG, blood pressure and cardiac output with both the one-third dose (2 g./kg.) and full doses (6 g./kg.) of urea during anesthesia in normothermic and in cooled animals.

## Method

Twenty experiments were conducted on 10 mongrel dogs ranging in weight from 9 to 15.5 kg. In half the dogs, a study was carried out at lowered body temperatures. Two weeks later, the dogs were studied for a second time at normothermia. This sequence was reversed for the other 5 dogs.

Anesthesia was induced with intravenous pentobarbital 25 mg./kg. A cuffed endotracheal tube was inserted, curare 0.07 mg. per kilogram 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 per minute 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 a slow intravenous infusion of 5 per cent dextrose in water begun in order to maintain patency. Cisterna magna puncture was performed with

TABLE 1. Cerebrospinal Fluid Pressure (mm.)

| | Normothermia | | | Hypothermia | | | |
|---|---|---|---|---|---|---|---|
| | Control | ½ Urea Dose | Full Urea Dose | Control | Hypothermia | ½ Urea Dose | Full Urea Dose |
| | *A* | *B* | *C* | *D* | *E* | *F* | *G* |
| Mean | 121 | 70 | 36 | 93 | 77 | 55 | 18 |
| Std. Dev. | 15.6 | 19.8 | 29.6 | 27.5 | 27.8 | 25.9 | 22.3 |
| $SE_m$ | 5.2 | 6.6 | 10.0 | 9.2 | 9.3 | 8.6 | 7.4 |

*A–B, A–C,* $P < 0.001$, highly significant. *B–C,* significant. *D–F, D–G, E–G,* $P < 0.001$, highly significant. *D–E, E–F, F–G,* not significant.

a short 18-gauge needle and continuous cerebrospinal fluid pressure monitored via a spinal manometer. Care was taken to avoid loss of cerebrospinal fluid. Baseline cerebrospinal fluid pressure was recorded before each procedure.

In the hypothermic studies, the hair was clipped, and hypothermia induced by surface cooling until a rectal temperature from 28° to 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, the dye concentration was measured with a Waters densitometer and recorded on a Honeywell oscillograph. The densitometer was calibrated after each study, using the animal's blood and dye from the original bottle. 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, hematocrit levels were used to adjust the cardiac output determination to the control level. Arterial blood samples for *p*H and $P_{CO_2}$ were obtained at the same time. *p*H was determined using the Astrup AME-1 Micro instrument. $P_{CO_2}$ was determined using the Severinghaus electrode in a thermostatically controlled water bath. Urevert 2 g./kg., *i.e.,* one-third of the total dose, was administered over a 20 minute period. Ten minutes were allowed for stabilization of the cerebrospinal fluid pressure. Cardiac output, hematocrit values, blood pressure and cerebrospinal fluid pressures were again recorded. Urea, 4 g./kg., *i.e.,* the remaining two-thirds of the total dose, was then given over the ensuing 40 minutes and the

TABLE 2. Cardiac Index (liters/min./m.²)

| | Normothermia | | | Hypothermia | | | |
|---|---|---|---|---|---|---|---|
| | Control | ½ Urea Dose | Full Urea Dose | Control | Hypothermia | ½ Urea Dose | Full Urea Dose |
| | *A* | *B* | *C* | *D* | *E* | *F* | *G* |
| Mean | 3.39 | 3.87 | 3.62 | 3.63 | 2.11 | 2.50 | 2.09 |
| Std. Dev. | 1.29 | 1.13 | 0.99 | 1.65 | 0.71 | 1.27 | 1.21 |
| $SE_m$ | 0.65 | 0.38 | 0.33 | 0.83 | 0.24 | 0.42 | 0.37 |

*A–B, B–C, A–C,* not statistically significant. *D–E,* significant. *E–F, F–G, E–G,* not statistically significant.

recordings repeated. The same procedure was followed with the dogs at normothermia.

Preliminary experiments with animals that underwent hypothermia before control studies had been obtained showed that they required active rewarming, prolonged assisted ventilation and relatively large amounts of intravenous fluids and electrolytes during recovery to replenish those lost in the excretion of the increased dose of urea.

## Results

Alteration of the order of procedures (hypothermia or normothermia) in the two groups did not affect the results.

*Cerebrospinal Fluid Pressure* (*Table 1*). Cerebrospinal fluid pressures were not elevated in hyperventilated anesthetized dogs in either study. The average cerebrospinal fluid pressure was reduced by hypothermia but the degree of reduction was not statistically significant. In both normothermia and cooled animals, 2 g./kg. and 6 g./kg. of urea significantly reduced cerebrospinal fluid pressures below control values. In the previous study the total dose of 1 g./kg. of urea significantly reduced cerebrospinal fluid pressure from resting values only in dogs that underwent hypothermia.

*Ventilation and Cerebrospinal Fluid Pressure.* Inasmuch as control values were not obtained before pulmonary hyperventilation, we cannot state what effect hyperventilation had on cerebrospinal fluid pressure.

*Cardiac Index* (*Table 2*). No alteration in cardiac index was seen in either group of dogs following urea administration. The cardiac index after cooling alone was found to be 45 per cent of the control value, a significant decrease. These results were comparable to those obtained in the first study in which it was found that hypothermia reduced the cardiac output to 60 per cent of the control value.

TABLE 3. Heart Rate

| | Control | Hypothermia | ½ Urea Dose | Full Urea Dose |
|---|---|---|---|---|
| | *A* | *B* | *C* | *D* |
| Mean | 138 | 77 | 77 | 77 |
| Std. Dev. | 27.8 | 26.0 | 18.0 | 17.6 |
| $SE_m$ | 8.8 | 8.7 | 5.7 | 5.6 |

*A–B*, $P < 0.001$, very highly significant. *B–C*, *C–D*, not significant.

*Heart Rate* (*Table 3*). Heart rate was significantly lower in hypothermic animals than in those with normal body temperature. The administration of 2 g./kg. or 6 g./kg. of urea did not alter heart rate in either group. Similar results had been obtained in the earlier study using a total of 1 g./kg. or urea.

*Mean Arterial Pressure* (*Table 4*). Unlike the results in the prior study, cooling significantly reduced the mean arterial blood pressure from 118 mm. of mercury to 92 mm. of mercury. However, the subsequent administration of urea did not significantly change this value, an observation obtained previously; no animal developed hypotension at any time.

*Venous Pressures.* Venous pressures were normal and without significant changes.

*pH and* $P_{CO_2}$. Control values for pH were elevated in both groups of animals following

TABLE 4. Mean Arterial Pressure (mm. Hg)

| | Normothermia | | | Hypothermia | | | |
|---|---|---|---|---|---|---|---|
| | Control | ½ Urea Dose | Full Urea Dose | Control | Hypothermia | ½ Urea Dose | Full Urea Dose |
| | *A* | *B* | *C* | *A* | *D* | *E* | *F* |
| Mean | 118 | 123 | 127 | 118 | 92 | 98 | 94 |
| Std. Dev. | 22.5 | 20.3 | 24.2 | 22.5 | 20.9 | 20.9 | 21.9 |
| $SE_m$ | 7.1 | 6.4 | 7.6 | 7.1 | 6.6 | 6.6 | 6.9 |

*A–B*, *B–C*, *A–C*, not significant. *A–D*, significant. *D–E*, *E–F*, *D–F*, not significant.

pulmonary hyperventilation. The mean value for animals at normal body temperature was 7.45 and for the cooled, 7.52. The $P_{CO_2}$ was 30.6 mm. of mercury in the ventilated non-cooled whereas mean values of 23.4 mm. of mercury were obtained following cooling. In these determinations temperature correction factors for $P_{CO_2}$ of blood *in vitro* were used.[4] No significant alterations in either measurements were found during urea administration.

*Hematocrit.* Duplicate hematocrit determinations showed little change despite the large amounts of urea given.

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

## Discussion

Urea in doses of ⅓ and 1 g./kg. was given to both normothermic and cooled animals during measurement of cerebrospinal fluid pressure in our earlier study. In the present series 2 and 6 g./kg. of urea were administered. Both groups of animals were anesthetized and the lungs hyperventilated. The dose of urea that brought about a significant reduction of cerebrospinal fluid pressure in cooled animals lay between ⅓ and 1 g./kg.[1] The dose which brought about an equal response in normothermic dogs lay between 1 g. and 2 g./kg. (table 1).

The combination of hypothermia and hyperventilation usually provides adequate conditions for intracranial operations. If with these measures the brain is still under considerable pressure, urea may be given intravenously. When the patient is cooled, one third of the usual dose administered at normothermia will ordinarily suffice to render the brain smaller. In the case cited in the introduction in which the full dose of urea was administered to a cold patient, cardiovascular collapse followed. A personal communication from Dr. James E. Eckenhoff tells of three similar clinical cases in which the full dose of urea was administered. All three developed severe arterial hypotension, one died and two recovered. Complete documentation of cause and effect is unavailable.

Our experiments with healthy dogs to whom urea was administered in a dose of 6 g./kg. of body weight during hypothermic anesthesia have provided no explanation for the circulatory collapse which occurred in our patient, for we observed no circulatory embarrassment when the animals were either warm or cooled. Cooling alone produced some diminution in blood pressure, cardiac index and pulse rate, but administration of urea in any of the doses tried failed to lower these values. Concomitantly, the cerebrospinal fluid pressure was appreciably lowered after giving one third the dose of urea, and dropped further after administration of the larger dose.

## Summary

Urea was administered intravenously to anesthetized hyperventilated dogs in doses of 2 g./kg. and 6 g./kg. These doses were considered comparable in effect in reducing cerebrospinal fluid pressure to ⅓ g./kg. and 1 g./kg., respectively, in human beings. Circulatory failure was not observed in any of the animals. Cerebrospinal fluid pressure was lowered significantly with each dose level. Both cardiac output and heart rate were diminished by hypothermia but the administration of urea to hypothermic dogs did not alter these parameters further.

## References

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