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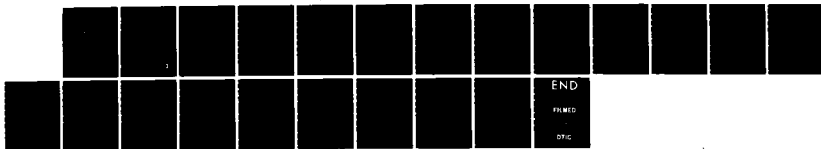
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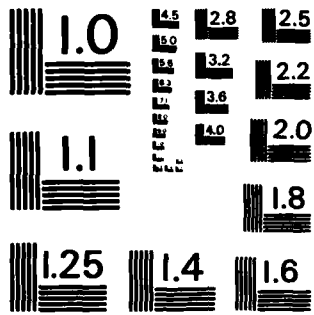
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**Altitude Exposure and the Role of Hypoxia and Arginine Vasopressin in Cerebral Fluid Dynamics**

**Annual Summary**

**Leo C. Senay, Jr.  
Daniel Tolbert**

**December 1, 1981**

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## SUMMARY

The overall objective of this research is understanding the influence of hypoxia upon the dynamics of rabbit and rat cerebrospinal fluid. The hypothesis to be tested is subdivided into two main questions: a) Does hypoxia lead to an increase in brain water and/or an increase in cerebrospinal fluid pressure; b) Does arginine vasopressin play a central role in the changes in cerebrospinal fluid dynamics when animals are exposed to reduced barometric pressures.

Through exposure of rabbits (10) to barometric pressures equivalent to that encountered at 18,000 ft. for 6-8 hrs. we have found no increase in the water content of various parts of the brain (temporal, parietal, frontal, thalamus, mid-brain, hind brain, cerebellum). We have found that the cerebrospinal fluid (CSF) pressure significantly increases when rabbits are exposed to hypoxia.

As yet, our results as to the influence of hypoxia upon arginine vasopressin (AVP) content of CSF are quite preliminary and indicate a surprisingly high concentration of AVP in rabbit CSF.

Difficulties with methodology have been time consuming and noted in the report.

We can conclude that the initial change in CSF dynamics with hypoxia is an increase in CSF pressure. At present, we do not know if this increase is due to an increase in CSF production and/or a decrease in clearance of CSF. The role of AVP in this process is under study.

### Foreword

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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### Statement of the Problem.

Upon exposure to altitude, certain individuals rapidly present signs of acute mountain sickness. The symptoms of this illness are suspected to be caused by an increase in intracranial volume and/or pressure. One portion of our research is aimed at revealing whether either or both of these events accompany exposure to hypoxia. There is evidence in the literature that arginine vasopressin within the cerebrospinal fluid may play a role in intracranial fluid dynamics. We propose to investigate the role of hypoxia and arginine vasopressin upon intracranial fluid dynamics in rabbits and attempt to separate out the roles of hypoxia and AVP through use of AVP deficient animals. This report contains results of initial experiments which bear upon the pressure/water content question with certain observations upon the arginine vasopressin content of rabbit CSF.

### Background.

When man rapidly ascends from low (< 5000 ft.) to high altitude (> 10,000 ft.), arrival at altitude is shortly followed by onset of acute mountain sickness (AMS) (1, 2, 3, 4, 5). Not all who ascend contract AMS and in those who do, the severity of symptoms appear to vary from individual to individual. If men with severe AMS cannot be returned to lower altitudes the course of the disability can end in death (1, 2, 4). In other subjects, AMS appears transient and the severity of the symptoms rather rapidly disappear with continued existence at altitude (6 and a host of others). Of concern in all cases whether reversible or irreversible is the degree of mental and physical incapacity suffered by those men contracting AMS. Slow ascension appears to prevent such symptoms (7), but in situations where slow ascent is not possible AMS may be as debilitating to certain populations (i.e., the military) as the shortage of water has proven to be in desert combat.

There is one general hypothesis as to the cause of AMS which appears to be supported by accumulated data. This is the hypothesis put forth by Hansen and Evans (2) wherein they postulated that the symptomatology is probably the result of either an increase in brain volume and/or an increase in intracranial pressure. Further, the cerebral edema (and symptomatology) occurs in spite of an overall reduction in total body water (3, 6, 8, 9, 10, 11). We are then presented with the curious state wherein total body water is depleted but simultaneously there may be an increase in CNS intracellular water. Since Hansen and Evans proposed their hypothesis, information has accumulated that suggests (a) how these shifts in body water at altitude may occur, and (b) a possible cause for the cerebral edema.

The hypothesis we propose to explore is as follows: Hypoxic exposure results in cerebral edema and/or increased intracranial pressure. The edema and pressure changes may be the result of:

1. A central action of arginine vasopressin (AVP) upon the function of the choroid plexus and, in combination with the lowered  $PO_2$ , alters cell membrane permeability in the CNS.
2. Alternatively - instead of triggering an increase in CNS AVP, hypoxia may suppress intraventricular AVP such that the transfer of CSF out of the intracranial compartment is reduced. With no

change in production, intraventricular pressures will rise. Hypoxia in concert with the increased intracranial pressure will cause changes in cell membrane permeability resulting in cerebral edema.

The overall aim of the proposed study is to investigate the role of arginine vasopressin in the cerebral events accompanying exposure to lowered partial pressures of oxygen.

The hypothesis is based on the following evidence. Improved methods of tagging various peptide hormones has supplied evidence for concentrations of AVP (antidiuretic hormone, ADH) at places within the CNS at some distance from the supraoptic and paraventricular nuclei as well as being remote from the posterior pituitary (12, 13, 14, 15, 16, 17).

More specifically, information now suggests a role for certain structures bordering the 3rd ventricle in body fluid homeostasis. Chief among these structures is the sub-fornical organ. Summy-Long et al. (15, 16) have shown that the sub-fornical organ of the rat not only contains a considerable amount of vasopressin (AVP) ( $44 \cdot 5$  pg/mg dry protein) but that the concentration of vasopressin doubled after 48 hours of water deprivation. How the vasopressin comes to be present in the sub-fornical organ is not known.

Intraventricular (IVC) injection of AII has been shown to increase plasma arginine vasopressin levels (18, 19, 20, 21, 22, 23). AII cannot cross the blood brain barrier and therefore the target of such IVC injections would have to lie outside this barrier. At least two logical choices exist: The SFO and the organum vasculosum of the lamina terminalis. Assuming a response to AII, SFO response to such stimulation could be either a direct release of AVP from local cells and/or possible neural influence on other nuclei containing AVP (such as the suprachiasmatic nucleus). It must be said that the response of periventricular tissue to AII is far from settled.

It does appear that the periventricular organs may play a role in body fluid balance (24, 25, 26). Here is a portion of the brain that has been shown to contain AVP, is responsive to AII, and increased osmolarity, increased  $\text{Na}^+$ , has neural connections with other AVP containing nuclei and stands with a foot in two camps, i.e., the blood and the CSF.

Finally, there does appear to be a relationship between acute mountain sickness and elevations in both plasma and urinary concentrations of AVP (1, 3, 27). Whether these increases are effects of the illness or are a causative factor in man awaits further experiments. Based on our diverse citations it appears plausible to suggest that the central changes in AVP may not necessarily reflect systemic changes in AVP (and vice versa).

The aim of the present proposal is to investigate the influence of hypoxia (simulated altitude) upon the production and action of AVP in the

cerebrospinal fluid. To gather such information, indwelling tubes must be placed in the third and lateral ventricles of the brain and, therefore some consideration must be given to the choice of experimental animal. The most crucial item is a sufficient amount of cerebrospinal fluid in order that radioimmunoassays of AVP can be accurately obtained. Cost and ease of handling are also considerations, and we have concluded that rabbits are the animals of choice for the studies wherein concentrations of CSF-AVP must be known, while an AVP deficient strain of rats should be used to separate the effects of hypoxia from AVP.

As subjects of high altitude research, there is much less known about rabbits than rats. However, two publications have appeared that caused us to select the rabbit (28, 29). Jain et al. found that the plasma volume of rabbits was significantly reduced at 6100 M but the other body water compartments were minimally affected. These results differ somewhat from the general findings in humans but even in human work there have been anomalous reports.

Next, Noto et al. (28) found that when injected into the lateral ventricles of normal rabbits, vasopressin lowered intracranial pressure. Intravenous acetazolamide also had a similar effect, and most interesting to us was that the effects of vasopressin and acetazolamide were additive. Suggestions have been made that acetazolamide affects production of CSF and now Noto et al. feel that AVP may influence passage of CSF from ventricles to cerebral veins via the arachnoid villi in rats. Evidence for the influence of AVP upon cell membranes and CNS capillary endothelium in monkeys has been reported (30, 31). Therefore, based upon the reports of Noto et al. and of Jain et al. and other considerations such as cost, upkeep, docility, etc., the rabbit seems to be an appropriate choice to investigate the relationship between hypoxic and intracranial fluid dynamics. The choice of the AVP-deficient rats (Brattleboro strain) to sort out the separate and combined effects of hypoxia and AVP on CNS fluid dynamics appears self-evident (4).

The first series of experiments is designed to gather information as to influence of hypoxia upon intraventricular AVP, and upon brain water content and cerebrospinal fluid pressure.

## METHODS

A. Cannula Implantation.

Male New Zealand rabbits (2-3 kg) were used in these experiments. Prior to surgery all animals were tranquilized with Rompum (Haver-Lockhart) and anesthetized with Ketamine hydrochloride (Bristol-Myers; 40 mg/kg). The animals were mounted in a modified rabbit stereotaxic head holder and secured in a Kopf stereotaxic apparatus. Lidocaine hydrochloride (2%) was injected subdermally at all pressure points. The juncture of the coronal and sagittal bony sutures (bregma) were aseptically localized through a midline scalp incision. Four mm lateral to the bregma, a 3 mm trephination was performed bilaterally exposing the underlying dura mater and cerebral cortex. Small (0-80 x 3/16") self-tapping stainless steel screws were implanted in the calvarium in front of and behind these openings. Stainless steel cannulae (21 gage, Plastic Products Co., Roanoke, VA) were perpendicularly mounted into the cortex, 4 mm lateral to the bregma. The entrance of the cannula tip into the lateral ventricle was indicated by the flow of sterile, mock CSF from a reservoir into the cannula. The roof of the lateral ventricle varied from 4 to 4.8 mm below the surface of the cerebral cortex. The bilaterally implanted cannulae were secured to the calvarium with cranio-plastic cement and the hollow cannulae were closed with a screw-down stylet. The skin flaps were drawn about cement islet and sutured in place. All implanted animals were closely monitored over a 4-7 day post-operative period.

1. Difficulties encountered. Early on it became evident that a successful implantation did not necessarily lead to a successful series of experiments. There were several problems:
  - a. In many instances, artificial CSF could be introduced into the ventricle, but the CSF produced by the animal would not percolate out of the cannula. A partial solution was to prepare a stylet slightly longer than the cannula and the final 2-3 mm of the stylet was displaced 30°. By introducing this device and by rotating, CSF would be caused to flow. We are not sure of the cause of such a valving effect but suspect tissue inclusions in the CSF.
  - b. In order to maintain cannulated rabbits over long periods of time wherein both CSF samples and pressure recordings are frequently obtained, we have found that if sterile technique is not observed during all such operations (gathering of CSF, measuring CSF pressures), then the animals succumb to infections in the brain which start within the cannulated ventricle. Not only had we to learn the proper techniques, but we also had to learn how to thwart the rabbits' ability to unscrew the stylet cap and remove the stylet from the cannula when the animal was in its home cage. Of course, such action was usually followed by a CNS infection. We now immobilize our

stylet heads with a bit of silastic cement.

- c. The order in which we learned these items had sterility last and as a result we lost a number of early animals to infection.

- B. CSF Pressure Recordings: If the recorder is placed external to the hypobaric chamber and if the pressure transducer is placed within the hypobaric chamber, and if the transducers are Statham gages, then these gages--or rather the contents of the cable leading from the chamber to the recorder--must be modified. The lead for a Statham gage has within it several polyethylene tubes which run from the recorder plug to the gage housing. This allows atmospheric pressure to be the reference pressure when recording. Such a set-up is rather adequate if one records at ambient pressure, but if the gage is placed in a hypobaric chamber and the other end of the transducer cable extends out of the chamber, then the reference pressure, while still remaining ambient (external pressure), causes extreme distortion of the metallic membrane of the transducer. We sealed off these hollow leads and thus our reference pressure is that within the hypobaric chamber.

Initially, we believed that we could record CSF pressure by simply leading the tubing from the CSF cannula to the transducer placed outside the hypobaric chamber. What we failed to realize at the time was that the rabbit was part and parcel of the hypobaric system and the moment we lowered barometric pressure within the chamber, the pressure recorded externally also rapidly became negative--indeed, exceedingly so. In such a situation, artificial CSF could be introduced into the rabbit at rates exceeding 1 ml/minute by simply connecting the rabbit to an external supply of artificial CSF.

Our present technique seems quite satisfactory. The transducer is exposed to the selected barometric pressure either before or after the rabbit has been attached. The transducer displacement so recorded is taken as zero. Fluctuations from the reading are then due to pressure changes within the CSF compartment when the rabbit is connected to the transducer.

- C. Collection of Cerebrospinal Fluid. Our early frustrations over patent cannulae (see A, above) also influenced our ability to collect CSF. Solving the patency problem has also solved our CSF collection problems. At present, we simply connect the implanted cannula to a small vial via Pg 50 tubing. The rabbit produces approximately 10-12  $\mu$ l of CSF per minute and thus in about 1½ hrs we can collect more than enough for RIA of ADH. We add that the ADH concentration does appear to be rather high in rabbit CSF and we therefore can perform an adequate analysis on smaller amounts (300  $\mu$ l), thus lowering collection time.
- D. Typical Pressure Experiment: After delivery, the New Zealand rabbits were allowed at least 2 days to become accustomed to their surroundings in the vivarium. Cannulae were then put in place (see A above) and, during the healing period, the rabbits were brought to the experimental

room, placed in a rabbit holder, and held there for 2-4 hrs, thus familiarizing them with the personnel and surroundings of the experiment. For control pressures (ambient barometric pressure), the animals were placed in the small animal hypobaric chamber and connected to the pressure transducers. Except for recording in the hypobaric chamber at ambient pressure, the externals surrounding the experiment were the same as those done at reduced barometric pressure, i.e., fan noise, air movement through valves, etc. At the end of the recording period, the rabbit was disconnected, removed from the chamber and an attempt was made to obtain a sample of CSF.

The same animal is brought back the next day and the experiment repeated, except that this time the rabbit is in a hypobaric environment. At the end of the recording day, the animal is removed from the chamber and a CSF sample is obtained.

The pressure readings obtained during animal recording are then compared with those obtained when the disconnected transducer is exposed to the same pressure as was the animal. The CSF pressures so calculated are then designated control for Day 1 and experimental for Day 2. The schedule calls for random exposure of the rabbits to barometric pressures set at 8,000 to 18,000 ft. at 2,000 ft. intervals.

- E. Brain Water: Unoperated animals were brought to the experimental room for 2-3 days in succession in order to reduce the stress of transport, new surroundings, etc. The animals were individually given a tranquilizer (Rompun) and then anesthetized with ketamine. The brain was then removed and sagittally sectioned into 2 halves. One half was quickly divided into pre-specified regions as determined by external landmarks. These regions were the temporal, parietal, and frontal cortices, thalamus, midbrain, cerebellum, and hindbrain. As each of the regions was obtained, it was quickly rinsed in normal saline, blotted and placed in a pre-tared weighing bottle. The remaining hemi-brain was treated as a unit and in the same fashion as the brain portions. The sections were weighed and then the water content was determined by drying 3 days at 75°C.

For experimental animals, a similar procedure was followed after the animals had been exposed to an ambient barometric pressure of 390 mm Hg ( $\approx$  18,000 ft.) for seven hr.

- F. Analysis for Arginine Vasopressin: The method is that of Robertson et al., J. Clin. Invest. 52: 2340-2352, 1973.
- G. Total Number of Animals: 51

## RESULTS

### CSF Pressures:

Typical responses of CSF pressure when the rabbits are exposed to altitude are illustrated in Figures 1 and 2. We do not have sufficient serial recordings at present (8,000; 10,000; 12,000 ft., etc.) to confirm or deny a relationship between exposure pressure and CSF pressure. We do know that our control pressures are similar to those published in the literature (28) and that an increase above control pressures invariably occurs when the rabbit is exposed to a hypobaric environment.

Note that at the end of the experiment, rapid pressure release results in a negative CSF pressure (compared to room pressure). Apparently, pressure equilibrium between the CSF and the environment is not particularly rapid. We have found that rabbits will usually return CSF pressures to at or near control levels but there are individual variations in the time span to accomplish this--not only among rabbits but also the same rabbit on different exposure days (see Figures 1 and 2).

### Brain Water Content:

In an initial report, we had sampled 5 control and 5 experimental animals and these preliminary data indicated that the water content of certain portions of the rabbit's brain was affected by hypoxia. With additional animals this did not prove to be true (Table 1). Under the experimental conditions, the water content of the various brain regions as well as an intact hemi-brain did not differ in control and those animals exposed to reduced barometric pressure.

### AVP Content of Rabbit CSF:

Our initial results as to the arginine vasopressin content of rabbit cerebrospinal fluid are inconsistent. Of the more than 40 assays, 28 indicate concentrations of AVP in rabbit CSF of greater than 20 pg/ml. We feel that these values are not accurate because of interfering substances in the CSF. Our method calls for extraction of plasma, i.e., mainly ridding the analysis fluid of protein but no extraction was recommended for CSF. Interestingly, as our cannulation techniques have improved, the apparent CSF concentrations of AVP have become less.

In our most satisfactory CSF samples, AVP concentrations have varied from 3 pg/ml to 11.4 pg/ml (12 assays on 8 animals) with a mean value of approximately 8 pg/ml. We also have found that there is a difference between extracted (deproteinized?) and unextracted CSF AVP values. Our extracted values are approximately 80% of our unextracted values. We are beginning to believe that this extracted/unextracted ratio is rather constant. If it does prove so, then we can apply a correction factor to unextracted CSF. This would allow us to work with 100 to 300  $\mu$ l of CSF in our assay. Considering that for extraction, 1 ml of CSF is needed, and further considering that the rabbit produces CSF at a rate of 10-12  $\mu$ l/min., the time saved would be considerable if we could use these smaller amounts for analysis. As yet, we have not the data base necessary to attempt manipulation of CSF AVP.

Table 1. Water Content (%) of Various Brain Regions and of Hemi-brains in Control Rabbits and Rabbits Exposed to a Barometric Pressure of 390 mm Hg for 7 - 8 hrs.

Region of Brain	<u>CONTROL</u>							
	Frontal	Parietal	Temporal	Thalamus	Mid-brain	Cerebellum	Hindbrain	Hemi-brain
$\bar{x}$	77.59	79.42	79.51	76.28	75.46	78.43	73.74	79.62
SD	1.3	1.79	1.76	1.53	1.68	1.01	3.27	.71
N	10	10	10	10	9	10	7	10
<u>EXPERIMENTAL</u>								
$\bar{x}$	79.46	80.23	80.79	76.98	75.84	78.81	74.16	79.87
SD	.68	.41	.77	.75	.87	1.21	.93	.42
N	9	9	9	9	8	9	7	9



Figures 1 and 2. Cerebrospinal fluid pressures (lateral ventricle) of a rabbit upon exposure to a reduced barometric in pressure. In Figure 1, B. P. = 570 mm Hg, and in Figure 2, 490 mm Hg.

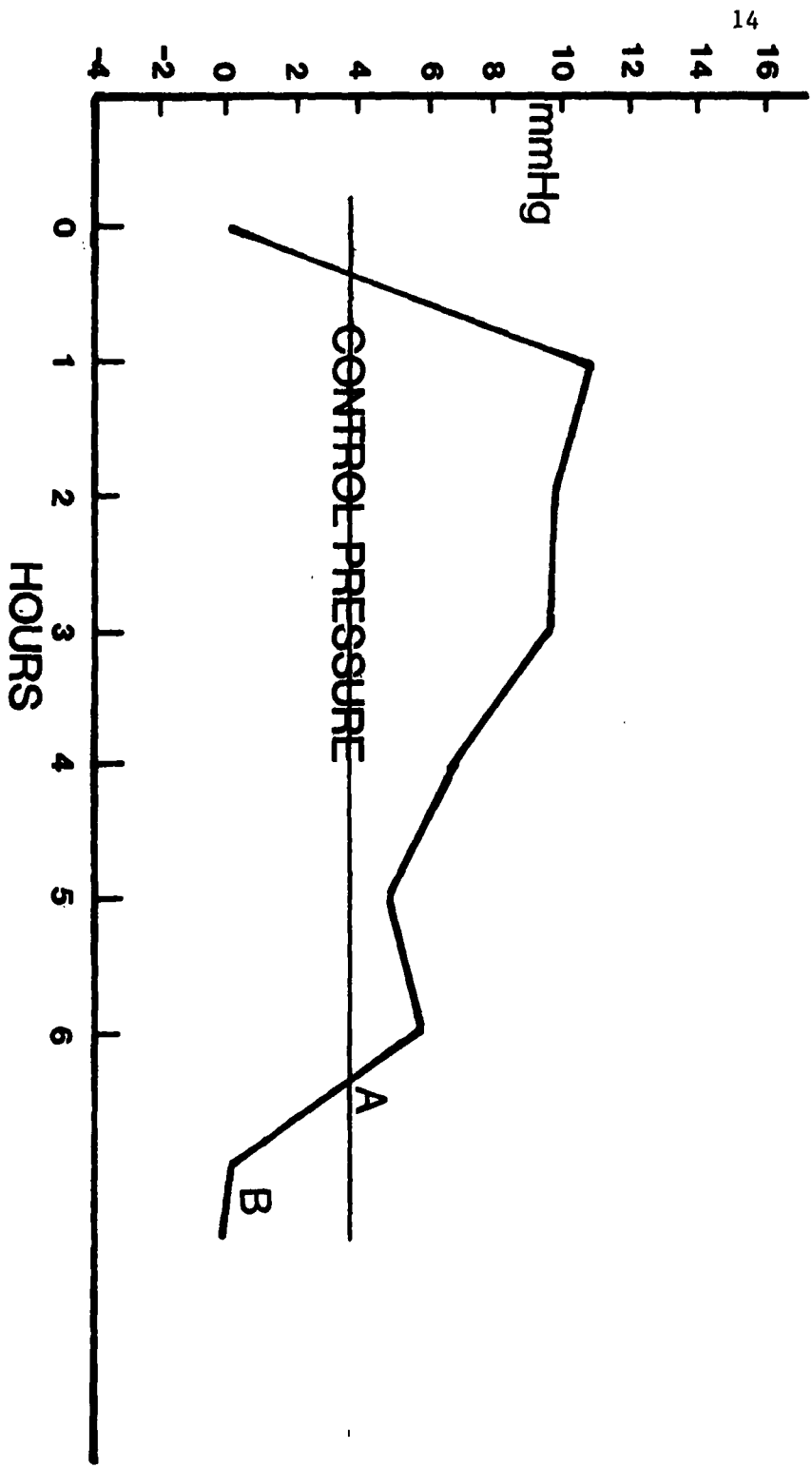


FIGURE 1

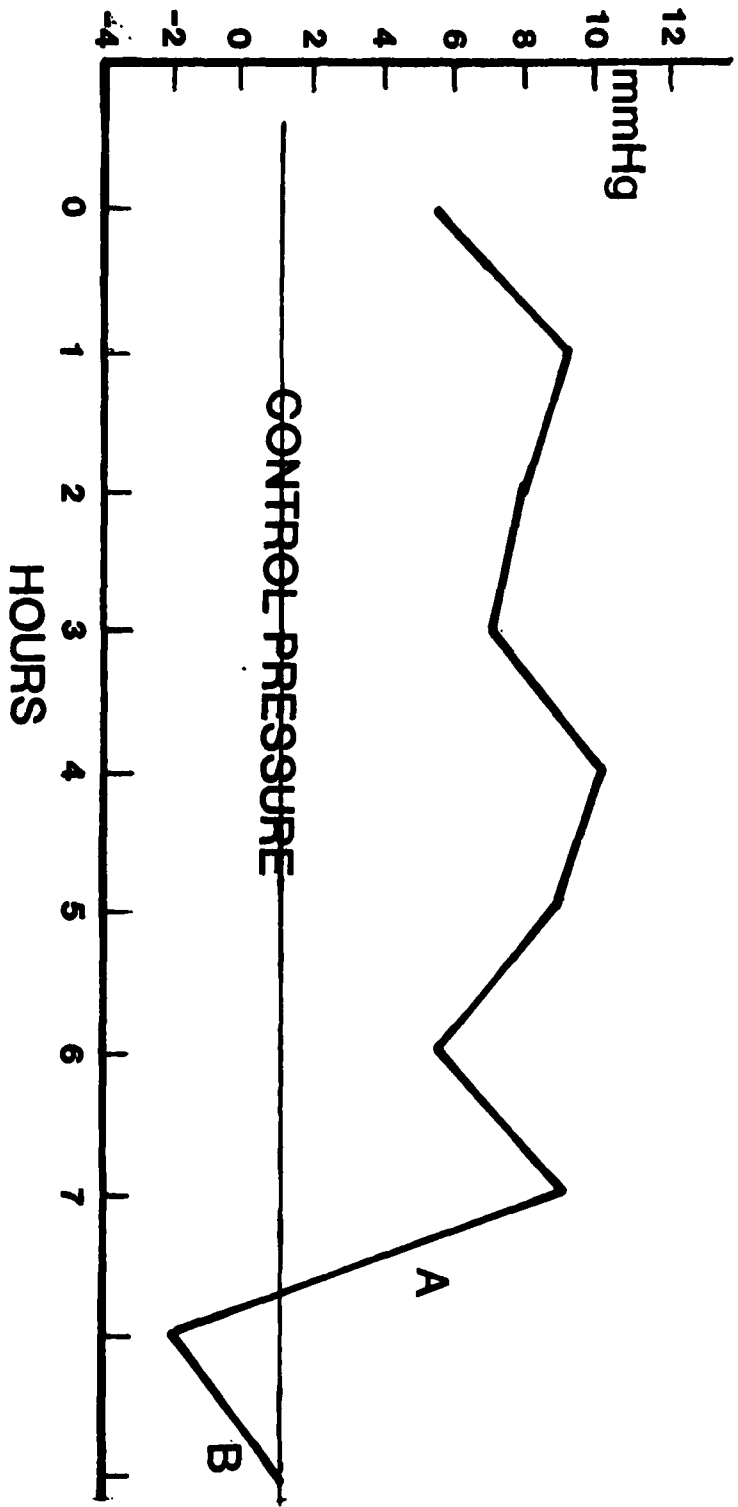


FIGURE 2

## DISCUSSION

This project is still in the development stage. However, we have established that exposure to hypoxia is accompanied by an immediate increase in CSF pressure. Increased brain water content does not appear to accompany this early (8 hr) increase in CSF pressure. As yet, we cannot make any statements as to the role of AVP in the pressure phenomenon.

### Recommendations:

We have established our techniques and believe that before the end of the first contract year we will begin to gather pertinent data as to the relationship of CSF AVP and the CSF pressure changes due to different stages of hypoxia. Once these results are obtained, we feel it would then be apropos to turn to pharmacologic manipulations of rabbit CSF production and drainage. This, then, could be done in parallel with our proposed Brattleboro rat study. (The rats have a genetic deficiency of AVP.)

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