Catecholamine response to intracranial hypertension

CARL J. GRAF, M.D., AND NICHOLAS P. ROSSI, M.D.

Division of Neurological Surgery and Division of Cardiovascular-Thoracic Surgery, University of Iowa School of Medicine, Iowa City, Iowa

Pulmonary congestion, hemorrhage, and edema, produced in the experimental animal by various methods of disturbing the central nervous system, have led to the concept that such neurogenically-initiated changes are mediated through the autonomic nervous system. Blocking the sympathetic nervous mechanisms prevents these changes. Little is found concerning the expected role of catecholamines. In this study, using a standard model of increasing intracranial pressure (ICP), intense cardiovascular changes, with blood pressure rising above 320 mm Hg and heart rate of 180 beats per minute, were noted. Within seconds, plasma catecholamine levels rose as much as 1200 times the highest normal values for epinephrine, 145 times for norepinephrine, and 35 times for dopamine. These changes occurred only when raised ICP was sustained and spatial compensation of the brain was exceeded. It is not unlikely that these events are related not only to increased ICP, but also to the effects of physical distortion of the brain stem with structural, functional, and vascular alterations within it.

KEY WORDS - intracranial pressure · plasma catecholamine · neurogenically-produced pulmonary change · spatial compensation · epidural balloon

The pulmonary changes of congestion, hemorrhage, and edema considered to be related to disturbances of the central nervous system have been produced in different species experimentally by various methods, such as intracarotid injection of saline,13 blunt head trauma,1,14 cerebral (hypothalamic) ischemia,16 intracisternal injections of veratrine,23 fibrin,18 thrombin and fibrinogen,4 intravenous epinephrine,24 and by various means of elevating intracranial pressure (ICP).5-7,9 These changes can be prevented by transection of the cervical spinal cord,5,6 alpha-adrenergic blockade,1,3 or deep narcosis.1,12,15 These observations have led to the formulation of the concept that neurogenically-produced pulmonary change is mediated through the autonomic nervous system and in particular by the sympathetic nervous system. One would expect to find a considerable amount of investigational work on the relation of catecholamines to such events. Actually, very little is present in the literature, no doubt due to the time-consuming and expensive methods that are currently available for the determinations of catecholamines in the blood. Using the method of producing increased ICP by means of an epidural balloon and having at our disposal the means of determining plasma catecholamines, we believe we have for the first time been able to show the exact temporal rela-
Catecholamine response to intracranial hypertension

tionships between intracranial hypertension and plasma catecholamines as well as the actual quantitation of the catecholamine levels.

Materials and Methods

Acute experiments were carried out in eight mongrel dogs weighing between 19 and 24 kg. These were lightly anesthetized with intravenous sodium pentobarbital (50 mg/cc) so that lid reflexes were preserved; the animal was able to breathe spontaneously but was yet able to tolerate an endotracheal tube. Mechanical ventilation was then instituted with a constant volume respirator* at 12 respirations per minute, and tidal volume at 350 to 400 cc, depending upon the weight and size of the animal. The dog was then laid on its right side and its head placed in the neutral position with vertex upward, taking care not to impede venous return from the head. An infusion of 5% glucose and saline (infusion rate 20–25 gtt/min) was given through a catheter placed in a femoral vein. A catheter was introduced into a femoral artery, attached to a Statham pressure transducer and led to a Beckman dynograph.t

The dog’s head was shaved, and a midline incision of the scalp made from the upper level of the orbits to between 2 and 3 cm behind the external occipital protuberance. The Bovie cutting knife was used to separate the pericranium and temporal muscles to make a wide exposure of the calvaria. In the right midparietal region a drill-well was made to accommodate the Richmond pressure bolt ~1 for recording the ICP. The dura mater and arachnoid were carefully opened, and a good flow of clear cerebrospinal fluid (CSF) assured. The bolt was then screwed into the skull, attached to Cobe tubing and connected to a Statham pressure transducer for recording on the polygraph. In the left midparietal area, a 1-cm burr hole was made to uncover the dura mater, which was then carefully stripped over an area from the inner calvaria sufficient to allow snug epidural placement of a Latex balloon with attached polyethylene tubing. Bleeding from the bone edges and dura mater was carefully controlled before the skull opening was sealed with dental cement. Extreme care was taken to assure that there was no leak of CSF at either the bolt or balloon sites. The animal was then left undisturbed for 30 minutes to attain a “steady state.” In two animals after the 30-minute period two samples (3 to 4 cc each) of femoral arterial blood were taken 1 minute apart for determination of baseline levels of plasma norepinephrine. In the remaining six animals, 3- to 4-cc samples of blood were taken from the femoral vein for baseline catecholamine assay. In each animal the ICP was then raised by injection of saline into the epidural balloon. The injection mass was such as to raise and sustain the ICP between 150 and 200 mm Hg. This was done by an initial injection usually of 6 cc of saline in 3 to 4 seconds. As the ICP fell to baseline, subsequent injections were made until the animal suddenly became severely hypertensive. In all animals this required a total balloon volume of 10 to 12 cc of saline. Samples of blood were then taken at 30- to 75-second intervals until the animal developed cardiovascular collapse; this usually took about 20 to 30 minutes.

The arterial samples were then taken with individual plastic syringes, transferred immediately to 6-cc rubber-stoppered plastic tubes containing 1% EGTA (ethylene glycol bis(beta amino ethyl ether) N, N° tetra-acetic acid with magnesium chloride), mixed by inverting the tubes 3 to 4 times, and placed in ice. The samples were then centrifuged in a refrigerated centrifuge at 2500 rpm for 10 minutes. Plasma was then carefully removed by pipette and frozen until assays for norepinephrine alone were made. (Determinations of plasma epinephrine and dopamine were not available at this laboratory.)‡ Samples were taken until the cardiovascular responses indicated imminent death of the animal. Because it was possible to obtain

---

*Harvard respirator manufactured by Harvard Apparatus, Inc., 150 Dover Road, Millis, Massachusetts.
†Statham pressure transducer manufactured by Statham Instruments Company, 2230 Statham Boulevard, Oxnard, California. Beckman Dynograph, type RM, manufactured by Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, California.
‡The determinations for norepinephrine in the arterial specimens were made according to the radioenzymatic method by Dr. Ranbir K. Bhatnagar, Department of Pharmacology, University of Iowa School of Medicine, Iowa City, Iowa.
determinations of plasma epinephrine and dopamine as well as norepinephrine in the Upjohn Laboratories, samples of venous blood were sent to that facility.

The venous samples of blood were taken with individual plastic syringes, placed in 5-cc glass, rubber-stoppered tubes containing 1% EGTA, mixed by inverting the tubes 3 to 4 times, and placed in ice. They were then centrifuged at 2500 rpm in a refrigerated centrifuge for 10 minutes to assure good separation of plasma. The plasma was carefully removed with pipette, placed in 3-cc plastic screw-type vials and frozen in dry ice for shipment by air within 36 hours. Initially, we used arterial blood for sampling. As arterial or venous sources of blood show no difference in values for plasma catecholamines and since it was more convenient to take venous than arterial samples, the venous source was selected.

Results

Sudden and extreme elevations of plasma catecholamines were observed within a few seconds of the elevation of the arterial blood pressure as a raised ICP was sustained. The arterial blood pressure in these instances would rise to 300 mm Hg, and the heart rate was in the range of 160 to 180 beats per minute (Fig. 1). The ratio of change of the catecholamine levels was 48.1 for epinephrine, 24.3 for norepinephrine, and 34.7 for dopamine (Table 1). This table represents the magnitude of change observed in the catecholamines associated with maximum blood pressure produced in the experiment. The ratio of the specific catecholamine reflects the magnitude of this change; for instance, epinephrine was increased an average of 48.1 times the base level. The range presented is a measure of variation which seems more appropriate for this study due to 1) the small sample size, and 2) the fact that the study is a descriptive observation. If a predictive model for catecholamine response was proposed then a large sample size and a more reflective measure of variation should be utilized. As the force and contractility of the heart declined, the blood pressure and the catecholamine levels declined concomitantly. Table 2 shows the mean and standard deviations.

A striking example noted in one animal of the temporal relationships of the elevation in

§In the venous samples, assay of catecholamines fractioned into norepinephrine, epinephrine, and dopamine was made by the radioenzymatic method in Laboratory Procedures, Division of Upjohn Laboratories, Woodland Hills, California, by Mrs. Geraldine Brown.

∥Normal plasma catecholamine levels measured by the radioenzymatic method are 0–55 pg/ml for epinephrine, 65–320 pg/ml for norepinephrine, and 0–90 pg/ml for dopamine.
Catecholamine response to intracranial hypertension

Fig. 2. Intracranial pressure was raised in increments until the point indicated by the vertical broken line, when spatial compensation was overcome. There was a simultaneous abrupt rise in blood pressure and heart rate with an intense release of catecholamines. This example is typical of the response observed in all animals.

Discussion

The method of raising ICP by means of an epidural balloon is one that is widely used. However, the ability of the brain to adapt itself to a rapidly expanding intracranial mass and thereby decrease ICP is not generally appreciated, although it has previously been well described by Langfitt, et al., Weinstein, et al. These workers suggested that this is accomplished by 1) reduction of the mass of the brain, made possible by its inherent plastic properties; 2) reduction of its blood volume by the compressive forces; and 3) redistribution of CSF. In every instance in our experiments, we noted that, when ICP was raised by means of an epidural balloon, this elevation could not be maintained until the balloon was further filled to the point where these compensating forces were overcome (Fig. 1).

It appears that Richardson and Woods in 1957 were the first to attempt measurement of plasma catecholamines under circumstances of increased ICP. They raised the ICP to 180 mm Hg for 1 minute by infusion of saline into the cisterna magna of dogs, and measured blood pressure, heart rate, myocardial contractility, and plasma levels of epinephrine and norepinephrine. They found levels in the range of 8000 pg/ml for norepinephrine and 5300 pg/ml for epinephrine. Bilateral adrenalectomy did not change the epinephrine levels in their dogs, but plasma concentrations of norepinephrine were significantly elevated (6300 pg/ml). Total preganglionic sympathetic block abolished the increments in these catecholamines.

Brashear and Ross studied the effects of alpha-adrenergic blockade with and without ganglionic blockade in mechanically ventilated dogs in which the CSF pressure was elevated by increments from 100 to 400 mm Hg. They found no change in plasma norepinephrine levels between the control period and the time when CSF pressure was raised to 300 mm Hg.

Turney, et al., in evaluating the sympathetic response in patients with head injury, noted that when ICP rose subsequent to elevations of PaCO₂, urinary catecholamine excretion was increased. Haider, et al., in a study of patients with severe cerebral trauma, found urinary catecholamine excretion to be increased, but there was no significant difference in such excretion when compared

plasma catecholamines, intracranial hypertension, and cardiovascular changes is seen in Fig. 2. All other animals reacted in the same way. At autopsy, the heart and the lungs appeared normal in all animals except this one, which showed severe intramyocardial hemorrhages (Fig. 3).
TABLE 1
Results of sustained increased intracranial pressure*

<table>
<thead>
<tr>
<th>Range</th>
<th>Base Level BP (mm Hg)</th>
<th>Peak Level BP (mm Hg)</th>
<th>ICP Level (mm Hg)</th>
<th>Epi (pg/ml)</th>
<th>Ratio†</th>
<th>Nor (pg/ml)</th>
<th>Ratio†</th>
<th>Dopa (pg/ml)</th>
<th>Ratio†</th>
<th>Time to Peak BP (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>average</td>
<td>148</td>
<td>300</td>
<td>99</td>
<td>20,610</td>
<td>48.1</td>
<td>5763</td>
<td>24.3</td>
<td>1146</td>
<td>34.7</td>
<td>2.5</td>
</tr>
<tr>
<td>low</td>
<td>120</td>
<td>260</td>
<td>40</td>
<td>2540</td>
<td>9.8</td>
<td>1110</td>
<td>7.9</td>
<td>159</td>
<td>11.4</td>
<td>1.5</td>
</tr>
<tr>
<td>high</td>
<td>180</td>
<td>320</td>
<td>150</td>
<td>36,140</td>
<td>239.3</td>
<td>10,060</td>
<td>79.2</td>
<td>2120</td>
<td>88.3</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*BP = blood pressure; ICP = intracranial pressure; Epi = epinephrine; Nor = norepinephrine; Dopa = dopamine. Note that there was wide variation in levels of ICP at which blood pressure peaked. Blood pressure would peak on the average of 2.5 minutes following last injection of saline into epidural balloon. Values in this table for catecholamines are not absolute; actual values in one experiment are illustrated in Fig. 2.
†Indicates ratio of the level of catecholamines to baseline level at the time of initial peak of blood pressure.

TABLE 2
Mean and standard deviations in catecholamine levels

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Baseline Level</th>
<th>Peak Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>epinephrine</td>
<td>428 ± 282</td>
<td>20,610 ± 13,896</td>
</tr>
<tr>
<td>norepinephrine</td>
<td>237 ± 125</td>
<td>5763 ± 3750</td>
</tr>
<tr>
<td>dopamine</td>
<td>33 ± 32</td>
<td>1146 ± 822</td>
</tr>
</tbody>
</table>

Fig. 3. Intramyocardial hemorrhages in one of the animals.

to that in generally traumatized patients. Brackett* made determinations of the degradation products of catecholamines in the urine as an index of autonomic nervous system activity in patients with head injury. The range of values was great among these patients, but the values in patients who had an associated injury to the cervical spinal cord were significantly below those with head injury alone. Smazhnova,† in a study of patients with closed head injury, found sharp increases in adrenalin and decreased levels of noradrenaline on the first day after injury, and a sharp rise in noradrenaline and a fall in adrenalin levels on the second day. These reports constitute the bulk of reported observations on catecholamines both clinically and experimentally under circumstances of intracranial hypertension or head injury.

Our studies indicate that plasma catecholamine levels are suddenly raised by increasing ICP, and that these elevated levels are temporally related to the sudden changes noted in the cardiovascular system, namely, increase in heart rate and blood pressure. No rise in the levels of plasma catecholamines was evident unless intracranial hypertension was sustained, and spatial compensation was overcome. No particular level of raised ICP appeared to be critical for this effect. More important was the overcoming of the process of spatial compensation. Very likely in overcoming this adaptability of the brain, forces of mechanical distortion, compression, displacement, and torsion are produced in some proportion which induce a functional nervous-vascular alteration, probably at the level...
Catecholamine response to intracranial hypertension

of the mesencephalon or medulla oblongata, to stimulate a catecholamine release. It is possible that the catecholamine release, which was demonstrated to be temporally related to the cardiovascular events, may not be related to the elevations of ICP alone but also to the manner in which the ICP acts upon the brain stem, that is, the degree and the way it is distorted with structural alterations and changes of blood flow within it.

Acknowledgments

We wish to express our thanks and appreciation to the Upjohn Company, Kalamazoo, Michigan, which made this study possible. We are grateful to Mrs. Geraldine Brown of Laboratory Procedures, Woodland Hills, California, Upjohn Company, and to Dr. Ranbir Bhatnagar of the University of Iowa, Department of Pharmacology, who patiently made the catecholamine determinations. Particular thanks are due to Mr. Alan Cipperon of the Medical Sciences Liaison Unit (Central Nervous System Diseases) of the Upjohn Company. We gratefully acknowledge the cooperation of Dr. Charles Hawker, Laboratory Director and Head (Research and Development), Kalamazoo RIA Laboratory, Dr. Sol Notrica, and Dr. Otto Klinger of Laboratory Procedures. We are further indebted to Mr. James Torner, graduate student in Biostatistics, Department of Neurology, the University of Iowa, who made the statistical analyses in these experiments.

References

19. Smazhnova NA: Changes in activity of the sympato-adrenal system in closed cranio-
cerebral trauma and trauma to the osteoarticular apparatus.} Ortop Travmatol Protez 34:13–17, 1973 (Rus)


Address reprint requests to: Carl J. Graf, M.D., The University of Iowa School of Medicine, Department of Surgery, Iowa City, Iowa 52242.