Catecholamine response to a gradual increase of intracranial pressure

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The association between raised intracranial pressure (ICP) and hemodynamic changes has been known for a long time. In 1866, Leyden described a rise in systemic arterial pressure when ICP approached arterial pressure. In 1901, Cushing reported the clinical triad of systemic blood pressure rise, bradycardia, and respiratory irregularities (the Cushing response), considering it a significant compensatory mechanism by which flow in the vital centers of the brain could be maintained. Cushing and other investigators later showed that there were other possible hemodynamic changes associated with raised ICP, probably due to differences in the level and degree of brain damage and ischemia.

The exact mechanism by which intracranial hypertension leads to these hemodynamic changes remains unknown. The sympathetic nervous system appears to be important in their pathogenesis, since such changes can be prevented by transection of the cervical spinal cord, alpha-adrenergic blockade, beta-adrenergic blockade, clonidine administration, bilateral adrenalectomy, or chemical sympathectomy using ganglion blockers. Raised levels of circulating catecholamines have been demonstrated after head injury and subarachnoid hemorrhage, and have been shown to correlate with Glasgow Coma Scale scores and outcomes after traumatic brain injury. Graf and Rossi and Rosner, et al., showed the temporal relationship between acutely raised ICP and plasma catecholamine levels.

Under clinical conditions, intracranial hypertension very often develops gradually due to secondary neurological injury. We developed an experimental model both to induce brain death by increasing the ICP gradually and to study concomitant plasma catecholamine levels, showing the relationship between ICP, cerebral perfusion pressure (CPP), and the rise of circulating epinephrine and norepinephrine levels. These observations are of great clinical relevance since most donor hearts for transplantation are from brain-dead patients who have suffered progressive intracranial hypertension. Posttransplant cardiac failure may be due to, among other factors, a catecholamine excess causing myocardial lesions before excision of the donor heart.

Materials and Methods

Animal Preparation

Seven mongrel dogs, each weighing between 20 and 28 kg (mean 24 ± 3 kg), were used for this study. The
experiment was part of a larger protocol in which the effect of intracranial hypertension on myocardial structure and donor heart potential was tested.\textsuperscript{33} The dogs were premedicated intramuscularly with 0.25 ml/kg fluanisone (10 mg/ml) plus fentanyl (0.2 mg/ml). Anesthesia was induced with propofol (10 ml as a bolus with a maintenance infusion of 0.25 to 0.75 ml/min). After endotracheal intubation, the dogs were artificially ventilated with a mixture of 30% oxygen in air. End-tidal pCO\textsubscript{2} was continuously monitored by an infrared CO\textsubscript{2} analyzer and verified by frequent determinations of arterial pO\textsubscript{2}, pCO\textsubscript{2}, and pH; the minute volume ventilation was adapted to maintain an end-tidal pCO\textsubscript{2} between 25 and 30 mm Hg. Cannulas were inserted to monitor peripheral arterial blood pressure and left ventricular pressure. A Swan-Ganz catheter was inserted to measure the cardiac output at regular intervals. The electrocardiogram (EKG) was monitored continuously. Neurological examination was performed regularly to test brain-stem reflexes (corneal reflexes and pupillary response to light).

Increasing Intracranial Pressure

After exposure of the calvaria, a burr hole was made in each of the two parietal bones, 1 cm from the midline. On the right side, a small incision was made in the dura mater and a de Martel catheter was introduced parallel to the midsagittal plane into the central part of the lateral ventricle. Intracranial pressure was continuously recorded. On the left side, an epidural latex balloon attached to a catheter was inserted over the frontoparietal region. The burr holes were sealed with wax to ensure that there was no leakage of cerebrospinal fluid (CSF). During the experiments, there were no major problems with instability of ICP recording, and adjustments to the intraventricular catheter were rarely necessary. When a minor adjustment in the catheter position was needed, care was taken not to cause CSF leakage. The electroencephalogram (EEG) was monitored continuously from six subcutaneous electrodes.

After three baseline arterial blood samples were obtained for measuring catecholamines and enzymes (total and cardiac fractions of lactic dehydrogenase and creatine kinase) and a blood gas analysis, ICP was raised gradually. An infusion pump was used to introduce saline at a rate of 4 ml/hr into the epidural balloon until brain death occurred. There were three criteria for establishing brain death: 1) CPP (calculated as arterial blood pressure — ICP) was 0 mm Hg or less; 2) an isoelectric EEG was present; and 3) brain-stem reflexes were absent. Blood samples were taken every hour until the CPP had dropped to 50 mm Hg. When CPP was below 50 mm Hg, samples were taken for determination of catecholamine levels every 5 minutes and, when CPP was below 30 mm Hg, samples were taken every minute until the CPP became negative. The half-life of catecholamines is 2 to 3 minutes; the sampling time was therefore adjusted according to the changes in CPP and/or other hemodynamic parameters so as not to miss a possible catecholamine burst. Arterial blood samples were obtained for enzyme measurement every hour after the baseline samples. After brain death, the dogs were monitored for up to 4 hours. Finally, the hearts were perfused in situ with glutaraldehyde and excised for histological analysis. The brains were removed, fixed in 10% buffered formalin, and sectioned for gross and microscopic analysis.

Measuring Catecholamine Levels

Plasma catecholamine levels were determined as follows: 5 ml arterial blood was mixed with 100 \( \mu \)l of solution (9 gm ethylenglycol-bis(\( \beta \)-aminoethylether)-N,N'-tetra-acetic acid, 6 gm glutathione, and 100 ml distilled water at pH 7). This was centrifuged at 2500 rpm for 5 minutes, then the plasma was removed and stored at -30°C to prevent breakdown of catecholamines until they could be assayed using high-performance liquid chromatography.

Statistical Analysis

Values are given as mean ± standard deviation. Polynomial regression was used to describe the catecholamine serum levels when compared to ICP and CPP. A p value of less than 0.05 was considered to be statistically significant.

Results

Hemodynamic Responses

After insertion of the latex balloon epidurally, there was a slight increase in ICP, which returned to baseline values within 10 minutes. After the constant infusion of saline at 4 ml/hr was begun, there was a steady rise in ICP until brain death was established and the infusion pump was stopped. The average volume required to induce brain death was 10.5 ± 1.7 ml. The ICP reached 135 ± 36 mm Hg at the point of brain death, at a mean of 158 ± 26 minutes after starting the infusion.

Initially, a normal pattern was observed on the EEG and brain-stem reflexes were present in all dogs. When CPP dropped to below 50 mm Hg, a gradual flattening of the electrical signal was observed until it became isoelectric. When CPP was in the low-positive range (20 to 30 mm Hg), all dogs showed unilateral mydriasis, with an evolution to bilateral mydriasis and absence of corneal reflexes when the CPP became negative.

Hemodynamic changes with this protocol are described extensively elsewhere.\textsuperscript{33} When CPP was in the low-positive range, there was a rise in arterial blood pressure and a slowing of the heart rate (the Cushing response, although respiratory changes could not be observed since the dogs were mechanically ventilated). This response was followed by a hyperdynamic state (increased cardiac output, tachycardia, arterial hypertension, and hyperpyrexia), which reached a maximum shortly after brain death was established (CPP ≤ 0 mm Hg). Although a gradual decrease in the hemodynamic parameters was observed in the period after brain death, no hemodynamic collapse occurred, even after several hours. Figure 1 shows the mean arterial blood pressure, ICP, and CPP from a typical experiment. Although all
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**Fig. 1.** Mean arterial pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), and catecholamine (epinephrine and norepinephrine) levels in a single experiment. The continuous inflation of the epidural balloon with saline (4 ml/hr) starts at 100 minutes (arrow).

**Fig. 2.** Mean serum levels of epinephrine and norepinephrine versus cerebral perfusion pressure (CPP) in seven dogs. Standard deviation (vertical bars) is shown for results in the lower range of CPP only. Catecholamine levels began to rise in the low-positive range of CPP and reached a maximum when the CPP became negative. Mean epinephrine and norepinephrine levels rose 286-fold and 78-fold, respectively, from less than 0.025 ng/ml to 6.867 ± 0.979 ng/ml for epinephrine and 1.865 ± 0.246 ng/ml for norepinephrine.

The catecholamine levels started to rise when CPP was between 20 and 30 mm Hg and reached a maximum just after the CPP became negative (p < 0.001). Temporally, this catecholamine release corresponded well with the observed hemodynamic changes.

**Discussion**

The method of raising ICP by means of an inflated epidural balloon is widely used. Gradually increasing the volume of the balloon allows for accommodation of the intracranial contents through redistribution of CSF, reduction of the intracranial blood volume, and reduction of the mass of the brain, which is made possible by its inherent plastic properties. This explains why the ICP began to increase only after a certain volume was infused into the balloon and spatial compensation was overcome.

Temporally, the hemodynamic changes corresponded with and were probably caused by the rise in catecholamine levels (Fig. 1). There was no correlation between the absolute value of ICP and the hemodynamic changes or catecholamine burst. These correlated well with the course of the CPP: both hemodynamic changes and increased catecholamine release started in the low-positive range of CPP (20 to 30 mm Hg) and reached a maximum when the CPP was negative (Fig. 2). This indicates that ischemia in certain areas of the brain is a primordial factor in the secretion of catecholamines as a reaction to raised ICP.

In 1978, Graf and Rossı showed a temporal relationship between acutely elevated ICP and the secretion of catecholamines. Both hemodynamic changes and release of catecholamines occurred only after spatial compensation of the intracranial contents was overcome and a raised ICP was sustained. According to their data, CPP was about 50 mm Hg when the cate-
The catecholamine burst was initiated. This does not correspond with our findings, in which CPP was lower (20 to 30 mm Hg) when the catecholamine burst started. A possible explanation of this difference between findings is the time factor. When the ICP is elevated gradually by inflation of a supratentorial epidural balloon, there is time for maximum spatial compensation and there is a rostral-to-caudal progression of ischemia. While there may be pressure gradients under these conditions, they will be minimal, and supratentorial ICP and CPP will reflect CPP in the brain stem. When the ICP is raised acutely, spatial compensation will be less complete and compartmentalization of the intracranial space may occur because of herniation of cerebral tissue through the tentorial incisure. This in turn may lead to local ischemia in parts of the brain stem due to compression and distortion. Therefore, the supratentorial measurement of ICP and CPP will be less predictive for the actual CPP in certain areas of the brain stem, in which CPP may be lower.

Rosner, et al.,29 investigated the catecholamine response to fluid-percussion brain injury. They reported a huge increase in epinephrine and norepinephrine levels within 10 seconds of injury, with a subsequent initial logarithmic rate of fall. Catecholamine release was directly related to injury severity, but as in our experiments there was a poor correlation between ICP and catecholamine levels. In the work of Rosner, et al., there was a high correlation between peak catecholamine release and peak arterial blood pressure ($r = 0.86$ for epinephrine), and ICP correlated with arterial blood pressure at 100 seconds postinjury; however, from the data available, it is impossible to see whether there was a correlation between catecholamine release and CPP.

Both Graf and Rossi11 and Rosner, et al.,29 reported a progressive decline in arterial blood pressure after the initial rise, while serum catecholamines were still elevated. Eventually the dogs died from cardiovascular collapse11 due to decreased myocardial function. This did not happen in our experiments: the dogs were monitored for up to 4 hours after brain death and, although there was a gradual decrease in hemodynamic parameters, there was no hemodynamic collapse. This is probably due to the lower peak levels of circulating catecholamines in our study. In another experimental setup,5 we were able to show that in dogs with acutely raised ICP the catecholamine levels are significantly higher than when the ICP is raised progressively, and that the myocardial damage probably caused by the catecholamines is more extensive when ICP is raised acutely rather than gradually. This coincides with the finding of Rosner, et al., that animals with light brain injury and a correspondingly lower catecholamine peak showed no progressive decline of arterial blood pressure.

The pathogenesis of increased catecholamine secretion induced by decreased CPP is not entirely clear yet. From animal experiments, it is known that stimulation of the dorsomedial and posterior nuclei of the hypothalamus leads to activation of the thoracolumbar autonomic outflow and an acute elevation of sympathetic tone.3,10 Stimulation of the anterior hypothalamus seems to lead to vagal activation.14 Both pharmacological and clinical studies have shown that cerebral ischemia activates both sympathetic and vagal systems (probably through release of inhibitory control), with the vagal effect usually predominating.1,17 This is confirmed by the work of Schrader, et al.,26 in which radioactive microspheres were used to study tissue blood flow in progressive intracranial hypertension. The hyperdynamic state (which in our experiment was related to catecholamine release) was observed only after the descending ischemia in the brain stem reached the area of the nucleus ambiguus in the medulla oblongata, causing a functional vagotomy whereby only sympathetic activation remained. Hypothalamic-cerebral autonomic transmission involves both polysynaptic and direct pathways to the intermediolateral gray zone in the thoracic spinal cord, from whence originate the preganglionic sympathetic nerves.20,22 The origin of circulating catecholamines is attributed to discharge at sympathetic nerve endings and to release from the adrenal medulla. The higher levels of epinephrine as compared to norepinephrine content suggest a predominating adrenal release, which confirms the findings of Graf and Rossi11 and Rosner, et al.,29 In clinical studies, the rise of norepinephrine levels always seems to be more important than the rise in epinephrine.1,7,12,18 This is probably due to the fact that there is a continued release from noradrenergic nerve terminals and that the release from the adrenal medulla is more limited in time.29

Conclusions

The sympathoadrenal response to a gradual increase of ICP is correlated with CPP and occurs when the CPP is in the low-positive range, reaching a maximum when the CPP becomes negative and dropping to baseline levels later. The fact that this catecholamine burst is related to the CPP rather than to the absolute value of the ICP suggests that ischemia in certain parts of the brain stem is a primordial factor in the increased release of catecholamines. Temporally, the observed hemodynamic changes correlated with the catecholamine burst and are probably caused by it. This means that the catecholamine burst can be considered to have a protective effect on the perfusion of vital areas of the brain. However, this may be very limited in time, since the catecholamines also cause myocardial damage that may eventually lead to a cardiovascular collapse. It is important to consider these data with regard to heart transplantation programs, since donor hearts for transplantation are often obtained from brain-dead patients who have suffered extensive central nervous system damage resulting in a gradual increase in ICP.

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