Vasospasm in response to repeated subarachnoid hemorrhages in the monkey

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This study investigates the relationship between vasospasm and repeated subarachnoid hemorrhages in 18 monkeys. Sixteen received weekly 4 cc injections of autogenous blood into the subfrontal subarachnoid space. The weekly mortality rate for 4 weeks was 6%, 33%, 20%, and 37% respectively. The over-all mortality was 75%. The degree of vasospasm did not correlate with the morbidity and mortality. Vasospasm was limited to the intradural cerebral vessels and was diffuse. It never lasted longer than a few hours, late vasospasm did not occur, and the degree of vasospasm did not alter with repeated occasions of "subarachnoid hemorrhage." Immediate electrocardiogram abnormalities were related to the height of the cerebrospinal fluid pressure rise following the subarachnoid hemorrhage (injected blood). Pathological examination of the vessels shown to be in spasm was normal. The study suggests that the increased mortality associated with repeated subarachnoid hemorrhage is due to cumulative structural damage rather than a heightened vasospastic response to repeated hemorrhages.

Because arterial spasm has been felt by many authors to be the principal cause of postoperative morbidity and mortality in patients with subarachnoid hemorrhage from ruptured aneurysms1 and since the mortality from repeated subarachnoid hemorrhage (SAH) at all intracranial sites is increased three or four times following a second hemorrhage,14 it seemed worthwhile to investigate the relationship between spasm and repeated hemorrhage in a controlled situation.

This study was designed to determine whether the quality or extent of the spasm changes in response to subarachnoid injections of fresh autogenous arterial blood made at weekly intervals.

Materials and Methods
To approximate the clinical situation as closely as possible, 18 adult female rhesus monkeys weighing between 2.6 and 6.9 kg were used in this study.

The animals were sedated with sodium pentobarbital 35 to 75 mg/kg body weight injected intraperitoneally approximately 3 hours prior to angiography. Intubation of the trachea with a flexometallic tube was carried out under direct vision. Tubocurarine 0.2 mg/kg was administered intravenously, and artificial ventilation begun. A Harvard variable volume ventilator and its associated animal ventilation graph (Kleinman and Radford) were used for this purpose. The predicted stroke volume necessary for
maintenance of a pCO₂ within normal limits was trebled and carbon dioxide added to the inspired vapor. The gases supplied to the reservoir for the ventilator passed through flowmeters and a “Fluotec” halothane vaporizer. They consisted of 4 liter/min of oxygen and carbon dioxide. The “Fluotec” dial setting was 0.75. Once artificial ventilation had begun, the system remained unaltered for the duration of the experiment; 30 minutes of ventilation were allowed for stabilization prior to angiography.

Cerebrospinal fluid pressure was monitored from a catheter in the subarachnoid space at the level of the third lumbar vertebra. The criterion for satisfactory placement throughout the period prior to the intracranial injection of blood was the association of clearly defined pressure fluctuations with respiration. Systemic arterial pressure was monitored from the catheter used to inject the contrast medium. Its tip was in the brachiocephalic artery. Blood pressure was therefore not recorded during the actual moments of injection of contrast medium and for a few seconds thereafter. Arterial blood for gas analysis was also obtained from this catheter. Statham transducers connected to appropriate preamplifiers and amplifiers (Electronics for Medicine) were employed. Cardiac rhythm was monitored from lead II. Permanent records were made on an Electronics for Medicine PR-7 recorder. Esophageal temperature was measured with a Yellow Springs thermometer. Astrup microtechnique was used to measure blood gases. This was done within an hour of sampling.

For angiography, a No. 6 French radioopaque polyethylene catheter (Rapol U.S.C.I.) curved tip, 80 cm long, lubricated with sterile silicone (Dow 555), was inserted through an arteriotomy in the femoral artery. Under fluoroscopic control the catheter tip was manipulated into the brachiocephalic artery proximal to the origins of the common carotid and vertebral arteries and a small test dose of Meglumine Iothalomite (Conray 60) injected to confirm its position. The animal was then placed on an Elema-Schonander biplane roll film changer and positioned with its chin flexed on a foam rubber holder. Great care was taken from week to week to maintain magnification factors constant at 1.3:1 for midline structures in both projections. For each angiogram, 8 ml of Meglumine were injected, using a Cordis I pressure pump at 400 lb/sq in. Simultaneous films were obtained in the anteroposterior and lateral projections at a rate of 4 per sec for 1.5 sec, 2 per sec for 2 sec, and 1 per sec for 2 sec.

Subarachnoid hemorrhage was simulated by the following method. A few days prior to each experimental series, a small skin incision was made in the scalp at a point in the midline 0.5 cm cephalad to the nasion. A twist drill hole was made at this point just large enough to permit passage of a No. 19 needle. Thus, each week when required, a needle 3 in. long with a short bevel was inserted through the skull in the midline under the frontal lobes along the floor of the anterior fossa. It was manipulated under x-ray control to a point just anterior to the tuberculum sella, lying in the subarachnoid space dorsal to the planum sphenoidale (Fig. 1). Lateral and anteroposterior x-rays were taken to confirm the needle's final position in each placement. Immediately, 4 ml of fresh autogenous blood were injected over a period of 20 sec and the needle withdrawn. Confirmation of injection of blood into the subarachnoid space was obtained at the time of the experiment by the blood staining of the spinal fluid in the lumbar catheter which was used to monitor spinal fluid pressure.

The animals were studied at weekly intervals. Sixteen of the animals received only blood injections, and two received only saline injections into the subarachnoid space. Studies were carried out at 1-week intervals. Of the 16 monkeys injected with blood, one was studied on one occasion, seven for 2 weeks, two for 3 weeks, and six for 4 weeks. Some animals also had angiograms carried out 24 hours following a subarachnoid hemorrhage.

At the start of each individual experiment, the monkey was anesthetized and the arterial cutdown carried out. Following ½ hour of anesthesia, a baseline angiogram was taken. The blood was then injected into the subarachnoid space and a second angiogram made between 1 to 15 min following this. A further period of recovery was allowed and then a third angiogram performed, usually about ½ hour after the first post-subarachnoid hemorrhage angiogram. Fol-
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Fig. 1. A. Lateral subtraction view of control angiogram. The sites at which measurements were made are indicated. B. Subtraction view of first post-SAH angiogram. The final needle position has been indicated by superimposing a cut-out of needle outline in scale. CA = intracavernous carotid; OP = carotid at origin ophthalmic; IC = carotid, intradural; PC = proximal pericallosal; DC = distal pericallosal; MC = middle cerebral; BA = basilar.

Following this procedure the femoral arteriotomy was closed and the animals extubated and returned to their cages. They were examined daily and their clinical state and weight recorded. The following week the same procedure was carried out except that the femoral cutdown site was alternated from one side to the other on alternate weeks. There were no cases of gangrene of the legs.

The films showing the best arterial phase on each angiogram were selected and the caliber of the arterial tree at various fixed points was measured in the anteroposterior and lateral projections using a calibrated hand lens with a fixed magnification and lens film distance. The circulation time was recorded for each series by calculating the interval between the first appearance of the contrast medium in the carotid artery to the time of good visualization of the parietal veins.

Animals dying during the experiment or immediate postoperative period were autopsied within a few days, those still alive after four subarachnoid hemorrhages were sacrificed within a few days following the final blood injection.

Following removal of the brains, detailed notations were made on the gross pathology. In addition, the fresh brains were photographed and then gross sections made and photographed. Finally, serial microscopic sections including the arteries and adjacent brain were stained with hematoxylin and eosin, Nissl, and Weigert’s elastic stains.

Results

Mortality and Morbidity in Response to Subarachnoid Hemorrhage

Of the 16 animals receiving blood injections, the mortality rate following each of the four injections was 6%, 33%, 20% and 37%, with an over-all rate of 75%. There were 43 weekly experiments in which blood was injected into the subarachnoid space and seven in which saline was injected in the same manner (two animals). There were
great variations in the post-experimental states of the different animals. Some monkeys showed virtually no evidence the following day of having had a subarachnoid hemorrhage. They were alert and eating normally. Other monkeys showed varying degrees of neurological deficit ranging from irritability and inactivity to profound coma. The degree of constriction at the intradural internal carotid and proximal pericallosal arteries during the first and second post-SAH angiograms was correlated with the clinical course of the animals at 24 hours. The degree of vasospasm in the animals which were dead the following day and the animals which were sitting up and eating normally was identical in the post-SAH angiograms (Fig. 2). The mean percentage change in vessel diameter within 15 min of the subarachnoid hemorrhage in the animals which were dead the following day was \(-33\%\), with a mean deviation of \(19\%\). The comparable figures for the animals alive and well the following day were \(-22\%\) and \(18\%\). The sample size in the dead group was 20 angiograms and in the alive group 64. The mean constriction in angiograms done between 15 and 45 min following the subarachnoid hemorrhage for the dead group was \(-23\%\) (mean deviation \(19\%\), sample size 20) and for the alive group \(-21\%\) (mean deviation \(19\%\) and sample size 66).

*Vessel Response to Subarachnoid Blood Injections*

*Location of Vasospasm.* Vasospastic responses are illustrated in Figs. 1 B and 3. A statistical analysis of the degree of spasm by location is shown in Table 1. There was no significant vasospasm in the intracavernous portions of the internal carotid artery. Blood caused significantly greater constriction of the intradural carotid artery than saline. The difference between the percentage constriction of the carotid intradurally and the basilar artery was significant at the 10\% level, with the carotid constricting more actively. In general, the vasospasm was diffuse but was maximal closest to the point of entry of the blood.

*Vasospasm in Response to Other Experimental Variables.* A statistical analysis was carried out on the significance of variance in data, including blood gas values, temperature, blood pressure, lumbar cerebrospinal fluid pressure and heart rate before and after subarachnoid hemorrhage over the course of the experiment. This showed that there was no significant change in the response of these parameters to the injections each week. The degree of spasm was also not significantly different from week to week. This analysis suggests that there was a stable experimental preparation without a significant alteration in any of the parameters measured at the time of the control angiogram and the first post-SAH angiogram.

*Vasospasm in Relation to Time.* Figure 4 illustrates that the spasm was greatest in the angiograms done soonest following the injection of subarachnoid blood. The mean percentage constriction in vessel diameter at 15 min was \(-24\%\), at 15 to 45 min \(-18\%\), at 24 hrs \(-2\%\), and at 7 days \(+6\%\). The

![Fig. 2. Percentage change of vessel diameter plotted against the clinical condition at 24 hours. The heading "< 15 minutes post-SAH" indicates the percentage of constriction on the first post-SAH angiograms done within this time interval; the 15 to 45 minutes post-SAH indicates the percentage constriction at the time of the second post-SAH angiogram. The crosshatched area indicates the 95% confidence level, i.e., points differing within this area would be expected to differ by this degree on the basis of chance alone 95% of the time.](image-url)
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Fig. 3. First angiograms, lateral views, taken after subarachnoid hemorrhage. A = first week, B = second week, C = third week, D = fourth week. There is variable constriction in the same monkey following subarachnoid hemorrhage which was maximal in week 2.

TABLE 1
Mean degree of spasm at selected arterial sites in all animals injected with either subarachnoid blood or saline measured as percentage change in baseline diameter

<table>
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<tr>
<th>Injection</th>
<th>CA</th>
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<th>PC</th>
<th>DC</th>
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<td>19</td>
<td>21</td>
<td>19</td>
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* Abbreviations for column headings: CA = intracavernous carotid; OP = carotid at origin ophthalmic; IC = carotid, intradural; PC = proximal pericallosal; DC = distal pericallosal; MC = middle cerebral; BA = basilar. Each figure is the mean % difference in caliber between the control and post-SAH angiograms at the sites given.

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was grossly marked of following tion and vasoconstriction of 92, SAH. An extreme prolongation of circulation th in the immediate response and that no significant vasospasm persists to 24 hours.

Vasospasm in Relation to the Number of SAH. Figure 5 illustrates the fact that the mean degree of constriction occurring following each subarachnoid hemorrhage showed no significant difference from week to week. The actual mean percentage constriction at week 1 was -21%, week 2 -16%, week 3 -19%, and week 4 -31%. The respective mean deviations were 19%, 14%, 23%, and 26%. The sample sizes were 54, 45, 30, and 24 angiograms. There was additional statistical evidence that the vasospastic response was not changed in any systematic manner on repeated hemorrhages. Analysis of the significance of variance in percentage vasoconstriction in the intradural arteries showed no significant difference in the degree of vasoconstriction from week to week.

Vasospasm and Circulation Time. A correlation was attempted between the percentage change in vessel diameter following subarachnoid hemorrhage and the change in circulation time. The correlation coefficient showed that there was no significant correlation between these two factors. Despite this, however, there were isolated incidents of extreme prolongation of circulation time in a few animals which showed the most marked degree of spasm.

Vasospasm in Individual Monkeys. There was grossly observable variation in the degree of vasospasm at the same time interval following SAH in many of the monkeys (Figs. 3 and 6). The basis for this is unclear since there was no significant variation in any of the experimental variables monitored, and the method of inducing SAH was apparently identical on each occasion.

Vessel Response to Subarachnoid Saline Injections

In the seven experiments in which saline was injected under the same experimental conditions as the autogenous blood, no gross vasospasm occurred. The analysis of the percentage change in vessel diameter is given in Table 1. The spinal fluid pressure responses to saline were virtually identical to that of blood, and this supported the view that vasospasm was not due to an alteration in intracranial pressure.

EKG and Hemodynamic Changes

In half of the experiments the animals had normal EKG's. In 20% there was a change in T-wave voltage of more than 25% or T-wave inversion. In 30% of the animals, other abnormalities were seen including QRS complexes that had an abnormal time relationship to the P wave or apparently occurred in the absence of a P wave. The data regarding CSF pressure, blood pressure, and heart rate in the period immediately before and following the peak rise of spinal fluid pressure following the blood injection showed that in the group with QRS changes the CSF pressure response tended to be significantly higher following the blood injections. These animals also had a greater elevation of blood pressure and a higher heart rate following the peak rise in CSF pressure.
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Fig. 6. Control angiograms, lateral views. A = first week, B = second week, C = third week, D = fourth week. There was no significant constriction in any of these angiograms done at weekly intervals on the same monkey just prior to injection of blood. In D there is perfect superimposition of the internal carotid arteries intradurally and extradurally with an apparent decreased diameter compared to the previous weeks in which slight rotation separates these arteries at the base.

pressure. Similar significant changes also occurred in the group that had T-wave changes only when these were compared to the animals which had no EKG changes. The peak CSF pressure for the animals with T-wave changes was identical to that of the animals with QRS changes. The QRS changes generally lasted only a few minutes whereas the T-wave changes were more persistent.

The mean CSF pressure in response to the 4 cc injection of either blood or saline usually exceeded the mean blood pressure for a few seconds but never for more than 10 sec. Within 5 min of these injections the CSF pressure had returned to close to base line values. In a few angiograms carried out on the crest of the CSF pressure wave, good intracranial filling was obtained. When this was done following the saline injections there was no evidence of vasospasm.

Pathological Changes

Detailed gross and microscopic examination was performed on each brain. Animals sacrificed immediately after subarachnoid blood injection showed diffuse subarachnoid hemorrhage (Figs. 7 left and 8 left). Those animals surviving several days after the final injection showed minimal residual subarachnoid blood. In those cases which survived several blood injections the subarachnoid space showed cellular proliferation with slight fibrosis and hemosiderin laden macrophages, in addition to recent mixed subarachnoid hemorrhage.

No vascular alterations were seen with routine or special histologic stains. In par-
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Fig. 7. *Left:* Brain specimen shows diffuse recent subarachnoid hemorrhage. *Right:* Brain specimen shows minimal hemorrhage remaining over the base of the brain after four subarachnoid injections of blood. A needle puncture site can be seen in the base of the frontal lobe on the right just medial to the olfactory nerve. The animal was sacrificed 3 days following the last subarachnoid blood injection.

In particular, there were no alterations of the elastica and no edema or fibrosis of arterial walls could be demonstrated.

Infarcts were found in nine animals. In some cases these had a border zone distribution, but in the majority they were located within the cortex in the area supplied by a middle cerebral artery. In only one case was embolic occlusion demonstrable in a feeding vessel. Some cases also showed infarcts within the striatum and amygdaloid nuclei. Several animals also showed multiple widely scattered recent focal ischemic lesions within the cortex. In two cases such lesions were prominent within the Ammon's horns of the hippocampal gyri. Approximately two-thirds of the recent cases showed ischemic neuronal change involving Purkinje cells of the cere-

Fig. 8. *Left:* Low-power, photomicrograph of cerebral convexity showing recent subarachnoid hemorrhage extending over convolutions and into sulcus. Nissl, ×7. *Right:* Section taken at the level of the tuber cinereum showing recent subarachnoid hemorrhage and the well-defined needle tract containing minimal hemorrhage, Nissl, ×7.
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bellum. In all animals dying spontaneously from subarachnoid hemorrhage, there was significant cerebral edema.

In seven animals the injecting needle was found to have perforated the basal aspect of a frontal lobe extending for a short distance within the cortex or subjacent white matter. Only minimal hemorrhage was present within the intracerebral needle tract and in no case was there perforation deep enough to enter a ventricle or to be anatomically related to the infarcts (Figs. 7 right and 8 right). Only one animal showed moderate hydrocephalus and it had died acutely following the second blood injection. It seemed unlikely therefore that the ventricular dilatation was due to the subarachnoid blood.

The two control animals showed no arachnoiditis or subarachnoid blood. One of the control animals, however, died shortly following the third experiment from a subdural hematoma. It had not shown any vasospasm even during the final experiment.

Discussion

Our experimental method differs in some respects from previously reported work in this field, particularly with reference to the method of inducing the subarachnoid hemorrhage. The technique of reinserting a needle through a twist drill hole has the advantage of eliminating the necessity of keeping a catheter permanently in position in the subarachnoid space over a period of weeks, which is extremely difficult.13 It obviates the possibility of damage to the cervical cord or medulla, which can occur with cisternal puncture.9 In addition, it more closely simulates the usual clinical situation resulting from the rupture of an aneurysm in the anterior circle of Willis. The successful subarachnoid instillation of blood was verified by the staining of the spinal fluid obtained from the lumbar catheter. The needle placement was verified radiologically to be constant from week to week. In two cases in which blood was injected intracerebrally there were obvious large, grossly destructive hematomas. In another animal in which an artery was punctured there was vigorous bleeding from the needle. The data from these experiments were discarded. The small needle tract through the basal tips of the frontal lobes was not felt to have a significant influence on the course of the experiment in which it occurred and was not associated with gross hemorrhage or necrosis. The technique of retrograde femoral catheterization14 for chronic studies seems to us to have distinct advantages over the method of leaving catheters implanted in the common carotid artery13 which seems likely to carry a continual risk of embolization and which alters the pattern of blood flow into the brain.

Since we carried out a brachiocephalic angigram in order to fill both carotids and the basilar artery, larger volumes of contrast medium were used than in previous studies.3,13,16,17 We were unable, however, to ascribe any morbidity or mortality to the contrast material as such. It is interesting to note the results of a study in humans in which a dilatation of 20% occurred in arteries, from 0.5 mm to 1 mm in diameter following a previous injection of contrast material.8 This suggests a possible source of error in all studies in which repeat angiography is carried out within short time intervals. If anything, however, it would have reduced the apparent amount of vasospasm that we observed. This factor would have been operative in a constant fashion throughout the series. Many of the limitations of the method of direct surgical observation12 are obviated with angiographic studies. Although a degree of accuracy in measurement is lost, the ease of carrying out chronic studies is greatly increased.

It appears to have been widely accepted that there is a direct casual relationship between the degree of vasospasm, frequency of infarction, and increased morbidity and mortality in humans and animals following subarachnoid hemorrhage. In one study13 some animals were observed that showed severe spasm without obvious neurological deficit whereas others showed neurological deficit without spasm. In a clinical study, when data regarding responsiveness and hospital mortality were compared in a series of patients with spasm and a series without, the differences were not statistically significant. Cases also occurred in which increasing spasm took place in the presence of clinical improvement.20 These observations are in

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accord with our demonstrations that the degree of vasoconstriction failed to correlate with the clinical course of these monkeys. There is, of course, impressive evidence for a strong association between spasm and increased mortality but evidence such as the above appears to indicate that there must be important variables in addition to angiographically demonstrated vasospasm in determining morbidity and mortality.

Since arterial pCO₂ was maintained relatively constant in this experiment, we were not able to demonstrate any direct influence on the vasospastic process. Elevating the pCO₂ appears to cause vasodilatation in spastic arteries in animals under conditions of hypothermia, in a preliminary report in patients with vasospasm, this also appeared to occur. On the other hand, alterations in pCO₂ did not result in a significant change in the character of the vasospastic response occurring as a result of mechanical stimulation in monkeys. It has been shown that the diameter of cerebral arteries in monkeys decreases from 6% to 10% at 30°C and 11% to 15% at 25°C; therefore, the insignificant change in temperature seen in our series would not appear to be of sufficient degree to account for the vasospasm observed.

The duration of vasospasm in our experiments is in accordance with that found in previous experiments in monkeys in response to subarachnoid blood injections. It seems generally agreed that spasm in response to blood seldom lasts longer than a few hours.

The high degree of variability in measurements of these small arteries in monkeys makes any theory of prolonged or late vasospasm in response to subarachnoid blood injections alone difficult to substantiate. Certainly our work fails to confirm that this occurs. One problem in the observations on biphasic vasospastic responses or late spastic responses has been that the influences of late increases in intracranial pressure do not appear to have been measured. In addition, the observation of Echlin that arterial puncture unaccompanied by subarachnoid bleeding does not produce prolonged vasospasm makes an acceptance of a purely mechanical hypothesis unwarranted. However, our failure in a large number of blood injections to produce any statistically significant late or prolonged spasm indicates with equal cogency that, since this does in fact occur in humans, factors in addition to subarachnoid blood must be operative; presumably some of these could be mechanical.

The degree of spasm that we observed seems to be comparable to that of most other studies. Significant spasm did not occur in the extradural carotid system. The carotid arteries were more spastic than the basilar artery, but the explanation of this was probably that more blood was in contact with the carotid system than the basilar system. Some workers have felt that the vertebro-basilar system did not contribute as actively to generalized vasospasm as the carotid system, but in experiments in which blood has been applied directly to the basilar, it has participated most actively in the spasm. It therefore seems as though the spasm is maximal at the site of application of the spasmodenic stimulus. One study indicated that the middle cerebral arteries had participated most actively in spasm even when the blood had been placed in the cisterna magna, but since this is an extremely small artery to begin with, we feel that observations regarding change in its caliber are subject to an even greater error than that which attends observations on the larger arteries.

The apparent variation in response of the arterial tree of individual monkeys to repeated blood injections has been noted by others and was apparent in some animals of our series. Presumably, the difference lies in unmeasured parameters such as the quantity of drugs present in the vessel and the blood injected, the biochemical response to the introduction of blood, minute anatomical difference in needle placement, and other unknown variables. This individual variation makes it necessary to regard any sweeping statements involving the etiology or therapy of vasospasm in the experimental state with some skepticism when they are based on solitary observations.

We did not find some of the changes such as necrosis of vessel walls, swelling of endothelial cells, and subendothelial polymorph permeation which have been seen in association with subarachnoid space hematomas in humans. The size of the hematomas in the subarachnoid space in monkeys did not ap-
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Bear to be sufficient to cause a structural spasm. Rupture of the internal elastic lamellae and loss of cellular detail in the media that occurred in arteries subjected to mechanical trauma with consequent spasm were not seen.

The pathogenesis of vasospasm in man probably involves the interplay of humoral, mechanical, neurogenic, and metabolic factors, which have varying importance in individual cases. Whether or not reduction in cerebral blood flow to given brain areas falls below critical levels probably does not depend solely on the diameters of major vessels. The tonus of the arterial tree distal to the radiologically observable arteries, the local pressure changes occurring intracranially, and general hemodynamic factors must also play crucial and concurrent roles. From this study it seems that the increased mortality due to repeated subarachnoid hemorrhages is due to cumulative structural damage rather than a heightened vasoplastic response to repeated subarachnoid hemorrhages.

Summary

Cerebral vasospasm was studied in 16 monkeys that received a weekly 4 cc injection of autogenous arterial blood in the subfrontal subarachnoid space for 4 weeks. The mortality rate for each of the 4 weeks was 6%, 35%, 20%, and 37% respectively, for an over-all mortality of 75%. The degree of vasospasm did not correlate with the morbidity and mortality and did not alter with repeated artificial subarachnoid hemorrhage. Vasospasm was limited to the intradural cerebral vessels, was diffuse, and never lasted longer than a few hours; late vasospasm did not occur. Immediate EKG abnormalities were related to the height of the CSF pressure rise following the subarachnoid hemorrhage. Pathological examination of the vessels shown to be in spasm was normal. The study suggests that the increased mortality associated with repeated subarachnoid hemorrhage is due to cumulative structural damage rather than a heightened response to repeated subarachnoid hemorrhage.

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