Effects of profound hypotension on cerebral blood flow during surgery for intracranial aneurysms

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The progression of changes in cerebral blood flow (CBF) and neurological status were measured in 12 patients in whom profound hypotension (mean arterial blood pressure (MABP): 30 to 40 mm Hg) was used during intracranial aneurysm surgery. Nine patients (Group I) showed autoregulation of CBF to an MABP of 40 to 50 mm Hg during surgery. None of these patients had arterial spasm preoperatively. Postoperatively, mild flow disturbances were noted at the site of retraction. Three Group I patients developed arterial spasm postoperatively, but there was no associated neurological deterioration. The remaining three patients (Group II) had impaired autoregulation during surgery, and CBF decreased by 35% to 65% at an MABP of 50 mm Hg. Two of these patients had angiography immediately before surgery, and both showed moderate to severe arterial spasm. Relatively severe flow disturbances were noted postoperatively at the site of retraction, and two patients developed ischemic deficits of late onset. Brain retractor pressure and the degree and duration of hypotension were equivalent in the two patient groups. There was no correlation between intraoperative reductions in CBF (to as low as 20 ml/100 gm/min in the unretracted hemisphere) and immediate postoperative neurological deficits. The use of halothane and mannitol and the relatively short duration of the flow reductions were suggested as factors contributing to the protection from ischemia that was observed. Arterial spasm was found to produce hemodynamic instability and reduced CBF, although neurological status was unaffected in the majority of patients. Patients with impaired autoregulation during surgery were at increased risk of delayed ischemic complications postoperatively, and showed characteristic flow disturbances at all three stages of their clinical course.

KEY WORDS - cerebral blood flow - controlled hypotension - cerebral vasospasm - cerebral aneurysm - subarachnoid hemorrhage

CONTROLLED hypotension has been used extensively in the surgical management of intracranial aneurysms in order to reduce the risk of intraoperative rupture and to facilitate surgery. A primary concern with the use of hypotension has been that cerebral blood flow (CBF) may decrease to critically low levels, resulting in ischemic damage to the brain. A large percentage of aneurysm patients will have had a recent subarachnoid hemorrhage (SAH). These patients frequently develop abnormal cerebrovascular reactivity and impaired autoregulation, suggesting that they may be more susceptible to severe flow reductions during hypotension than normal individuals.

Pickard, et al., have shown recently that patients with impaired autoregulation to moderate intraoperative hypotension (a mean arterial blood pressure (MABP) of 50 mm Hg) had increased risk of developing postoperative neurological deficits of late onset. Although this study demonstrated a strong correlation between hemodynamic instability and delayed neurological sequelae, the authors were unable to determine the cause of autoregulatory impairment or to determine the relationship between intraoperative CBF reductions and the immediate postoperative clinical status. It is possible that intraoperative ischemia may contribute to the incidence of postoperative neurological deficits in these patients; however, this remains unproven. Factors such as the extent of brain retraction and the degree and duration of hypotension would be expected to influence this relationship. Our own clinical experience indicates that reductions...
in MABP to 30 to 40 mm Hg for brief periods during surgery are well tolerated. There are no data in the literature describing alterations in CBF at these extreme levels of hypotension in normal man or, more importantly, in patients with SAH.

This report describes our initial experience with intraoperative measurements of CBF and brain retractor pressure during profound intraoperative hypotension. The results of these studies were correlated with pre- and postoperative neurological status, angiography, and CBF measurements.

Clinical Material and Methods

Nine patients with proven SAH and three patients with unruptured aneurysms were studied. Preoperatively, one patient was Grade III according to the classification of Botterell, et al.,5 (disoriented, with mild left weakness) and 11 were in Grade I. Eight of the aneurysms were on the basilar artery and the remainder were located on the middle cerebral, carotid-ophthalmic, posterior communicating, and anterior communicating arteries.

Anesthesia was induced with thiopentone and was maintained with fentanyl or alphathesin combined with controlled ventilation using a mixture of nitrous oxide, oxygen, and either halothane (10 patients) or enflurane (two patients). Muscle relaxation was achieved using pancuronium bromide. All patients had a lumbar cerebrospinal fluid (CSF) drain in place and were given mannitol (0.5 gm/kg) and, if required, furosemide (0.1 mg/kg) to facilitate brain retraction. An intra-arterial catheter was positioned in the radial or dorsalis pedis artery for continuous arterial pressure monitoring and intermittent sampling for arterial blood gases. Hypotension was induced by halothane alone in five patients, and a combination of halothane and sodium nitroprusside in seven patients. In two patients, enflurane was substituted for halothane. Brain retractor pressure was measured using a Codman retractor pressure monitor* in all patients.

Intraoperative CBF measurements were obtained using a modification of the intravenous xenon-133 (133Xe) injection technique.27 A single scintillation detector,† 1.5 in. in diameter with 3-in. collimation, was mounted under the parietal area of the skull contralateral to the side of craniotomy. An identical detector was used to monitor the end-tidal 133Xe concentration in a sample of air drawn from the endotracheal tube. The clearance curves were recorded on a Brinkmann two-channel recorder‡ for 10 minutes following intravenous injection of 4 to 5 mCi of Xe dissolved in sterile saline. The calculation of CBF with appropriate corrections for recirculation was carried out off-line on a PDP 11/60 computer. The CBF was calculated using both the initial-slope technique described by Wyper, et al.,27 and by conventional bicompartmental analysis.20,23 Determinations of CBF were carried out routinely at four intervals during surgery: 1) a control measurement at normotension; 2) during preliminary exploration of the aneurysm (MABP about 50 mm Hg); 3) during clipping of the aneurysm (MABP 30 to 40 mm Hg); and 4) at the conclusion of the operation when MABP had returned to normal. Each blood pressure level was maintained for at least 5 minutes before measurement was begun. In addition, 15 to 30 minutes were allowed to elapse following the administration of mannitol or furosemide before the next CBF determination was begun. These precautions were taken to avoid any transient flow alterations resulting from the change in MABP or the addition of drugs.

Seven patients had both pre- and postoperative inhalation CBF studies within 6 days of their surgery. The inhalation studies were performed using a 32-channel inhalation cerebrograph§ with 16 detectors positioned in a parallel array on each side of the head.4 For each CBF measurement, the patient breathed a mixture of 133Xe and air (3 to 5 mCi/liter) for 1 minute, followed by a 10-minute washout period. Expired air was sampled continuously from the face mask for determination of end-tidal 133Xe activity. Flow parameters were calculated using bicompartmental analysis as developed by Obritz, et al.30 Data acquisition and flow calculations were carried out on-line using a PDP 11/60 computer. Appropriate corrections for scattered radiation from the air passages were made according to a method devised in this laboratory. The correction technique is similar to that published by Risberg22 and will be reported separately. These corrections were found to be essential for the accurate determination of CBF in the temporal and frontotemporal regions immediately adjacent to the major airways. Blood pressure was measured by sphygmomanometer cuff, and both hemoglobin and arterial blood gases were measured using arterialized blood obtained by standard ear-lobe sampling techniques.

Results

Intraoperative Measurements

The intraoperative CBF results obtained with the 3-minute initial-slope method27 were compared to those using bicompartmental analysis of the 10-minute clearance, as suggested by Risberg, et al.23 The

* Codman retractor pressure monitor manufactured by Codman and Shurtleff, Peterborough, Ontario, Canada.
† Scintillation detector manufactured by Picker Corp., 595 Miner Road, Cleveland, Ohio.
‡ Brinkmann two-channel recorder manufactured by Brinkmann Instruments Corp., 50 Galaxy Boulevard, Rexdale, Ontario, Canada.
§ Thirty-two-channel inhalation cerebrograph manufactured by Novo Diagnostic Systems, Novo Alle, Bagsvaerd, Denmark.
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Fig. 1. Relationship between cerebral blood flow (CBF) and mean arterial blood pressure (MABP) for patients in Group I (left) and Group II (right). The CBF is expressed as a percentage of the control flow observed in each patient. The patients in Group II failed to autoregulate to the initial reduction in pressure.

The initial-slope method yielded a value for CBF which was consistently 10% higher than that obtained by Risberg's method (average difference 5.5 ± 1.3 ml/100 gm/min; mean ± SEM). However, when the changes in CBF were calculated as a percentage of the control value, there was no significant difference between the two methods. Although care was taken to maintain MABP constant during the 10-minute measurement period, this was not always possible during profound hypotension. In cases of extreme blood pressure fluctuations, the two-compartment model yielded a poor fit to the experimental data. Therefore, as suggested by Pickard, et al., the initial-slope index (ISI) was used as the primary method of analysis for the intraoperative CBF measurements.

The patients were divided into two groups based on their autoregulatory response to the initial reduction in MABP. Nine patients (Group I) demonstrated intact autoregulation as MABP was reduced from 76 ± 2 mm Hg (mean ± SEM) to 49 ± 2 mm Hg (Fig. 1 left). The CBF (calculated by ISI) increased in five patients and decreased slightly in four. All patients in this group showed a decrease in cerebrovascular resistance (MABP/CBF) of at least 20% (mean reduction 36% ± 4%) during moderate hypotension. As MABP was reduced further to 39 ± 1 mm Hg, flow remained essentially constant in two patients and decreased in the rest.

The remaining three patients (Group II) showed impaired autoregulation in response to the initial reduction in pressure. As shown in Fig. 1 right, CBF decreased markedly (35% to 65%) in response to a reduction in MABP from 78 ± 2 to 49 ± 1 mm Hg. Cerebrovascular resistance increased in all three patients (range 2% to 75%), indicating a lack of autoregulatory vasodilatation. During clipping of the aneurysm at an MABP of 40 ± 1 mm Hg, CBF increased slightly in two and remained constant in the third.

Figure 2 shows the relationship between CBF and MABP for each group during the control, hypotensive, and recovery phases of surgery. For patients in Group I, there was no difference (paired t-test) between the control CBF and CBF at moderate hypotension, or between control and recovery measurements. At extreme hypotension, CBF was significantly lower than the control value. For patients in Group II, CBF at both levels of hypotension was lower than
TABLE 1
Summary of preoperative status in this series

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
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<td>3</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
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<td>44</td>
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<td>range</td>
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<td>36-55</td>
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<tr>
<td>clinical Grade I</td>
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<td>3</td>
</tr>
<tr>
<td>clinical Grade III</td>
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<td>0</td>
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<tr>
<td>days after SAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>range</td>
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<td>2</td>
</tr>
<tr>
<td>arterial spasm</td>
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</tr>
</tbody>
</table>

During the recovery phase, CBF was lower than the control flow for all patients in Group II; however, the extent of flow depression was quite variable (range -5 to -34 ml/100 gm/min). Arterial pCO2 in Group I patients was 37 ± 2, 39 ± 3, 36 ± 2, and 38 ± 3 mm Hg during the control, exploration, clipping, and recovery phases, respectively. The corresponding pCO2 values in Group II patients were 39 ± 3, 30 ± 4, 30 ± 4, and 32 ± 3 mm Hg. With the exception of the control measurement, arterial pCO2 was slightly lower in Group II patients, although this was not statistically significant. Sodium nitroprusside was used in five of the nine Group I patients and two of the three Group II patients. Average brain retractor pressure was identical in both groups of patients (Group I: 20 ± 2 mm Hg; Group II: 20 ± 4 mm Hg) as was the duration of the exploratory phase (46 ± 6 and 42 ± 9 minutes, respectively) and the clipping phase (37 ± 5 and 35 ± 12 minutes, respectively) of surgical hypotension.

**Preoperative Status**

A summary of the preoperative status is shown in Table 1. The only major difference between the two groups was in the incidence of arterial spasm. Of the seven Group I patients with immediate preoperative angiograms (within 48 hours of surgery) none had arterial spasm, whereas both Group II patients were found to have moderate to severe spasm. The remaining Group II patient had shown severe narrowing of the basilar artery the previous week; however, the angiogram was not repeated.

**Postoperative Course**

Five patients in Group I had an uneventful postoperative course. (Cranial nerve palsies resulting from retraction during surgery have been omitted from analysis.) Two patients had surgical complications. In one patient, the aneurysm ruptured during clipping and severe edema developed. The patient was recovering when the aneurysm rebled on the 3rd postoperative day, causing death. The second patient developed a large postoperative extradural hematoma with a 3-cm midline shift, resulting in left hemiparesis. This cleared progressively following evacuation of the hematoma. The remaining two patients had transient postoperative complications. One patient was drowsy and disoriented on recovery from anesthesia, but was fully recovered within 48 hours. The second patient had a transient left drift and internuclear ophthalmoplegia which began approximately 12 hours postoperatively and resolved before discharge. Three Group I patients developed arterial spasm postoperatively; however, there was no associated deterioration in neurological status.

There were no intraoperative complications in Group II. One patient had an uneventful recovery, although moderate arterial spasm was present postoperatively. The remaining two patients both developed delayed neurological deficits approximately 1 week following surgery. One patient awoke from anesthesia with a mild left hemiparesis and was slightly drowsy but oriented until the 6th postoperative day, when he became stuporous. Angiography revealed that the clip had slipped and had occluded the basilar bifurcation; however, we are uncertain as to when this occurred. A computerized tomography (CT) scan showed a midbrain infarct. The patient improved immediately with volume expansion and progressively thereafter. The second patient was classified as Grade I for 12 hours, at which time she developed a sudden right hemiplegia. Angiography showed severe bilateral anterior cerebral artery spasm. She recovered completely with volume expansion and was well until the 8th day after surgery, when she suddenly became apathetic and nearly mute but remained oriented. A CT scan the following day showed bilateral mesial frontal lucencies.

We examined the relationship between the lowest value of CBF measured intraoperatively and the clinical status immediately on recovery from anesthesia in all patients without obvious surgical complications.
In patients who were alert with no deficit postoperatively, the lowest intraoperative CBF values ranged from 20 to 65 ml/100 gm/min (mean 43 ± 7 ml/100 gm/min). In those who were drowsy and/or had a deficit postoperatively, the intraoperative CBF values ranged from 23 to 57 ml/100 gm/min (mean 38 ± 12 ml/100 gm/min). There was no significant difference between these two groups.

Pre- and Postoperative CBF

Four Group I patients and all Group II patients had pre- and postoperative CBF measurements. All patients were alert and oriented at the time of both studies with the exception of one Group II patient who was slightly drowsy but oriented, with a mild left hemiparesis postoperatively. The mean hemispheric values of blood flow in gray matter (Fg) and the relative weight of the gray matter compartment (Wg) are shown in Table 2. Preoperatively, Fg was significantly depressed in Group II patients when compared to Group I at similar levels of arterial pCO2 (38 ± 2 and 39 ± 3 mm Hg for Groups I and II, respectively). There was no significant side-to-side asymmetry in either group. Postoperatively, all Group I patients demonstrated relative Fg hyperemia in the operated hemisphere when compared to the contralateral side (range 2 to 13 ml/100 gm/min). Group II patients did not show this hyperemic response and Fg was slightly lower in the operated hemisphere. In Group I patients, Fg remained higher than that in Group II. The corresponding values of arterial pCO2 were 37 ± 2 and 34 ± 3 mm Hg. There was a significant reduction in Wg in the operated hemisphere of both groups (paired t-test), whereas the contralateral hemisphere was largely unaffected. The most striking difference between the two groups of patients was demonstrated in the regional distribution of the Wg reductions in the operated hemisphere as shown in Fig. 3. Group I patients showed mild decreases in Wg of approximately 5% to 10%, accentuated in the temporal lobe which was the site of retraction in this group. In contrast, the Group II patients demonstrated moderate to severe reductions in Wg of up to 40% in the frontal and temporal regions corresponding to the frontotemporal retraction required in this group of patients.

Discussion

Two distinct groups of patients were identified based on their autoregulatory response to intraoperative hypotension. The majority of patients (nine of the 12 studied) showed intact autoregulation, and cerebrovascular resistance decreased appropriately as MABP was reduced. In this group, CBF remained relatively constant until MABP was reduced below 40 to 50 mm Hg. The remaining three patients showed a strikingly different response to hypotension in that CBF fell by 35% to 65% when MABP was reduced to 50 mm Hg. These results are very similar to those reported recently by Pickard, et al., although the cause of autoregulatory impairment in their patients was unknown. Griffiths, et al., found no net reduction in CBF during moderate hypotension (MABP 67 mm Hg); however, four patients (20%) had significant flow decreases. Nornes, et al., studied 21 patients with SAH and found lower autoregulatory limits of up to
85 to 95 mm Hg during intraoperative hypotension. None of these studies reported angiographic findings so that the incidence of arterial spasm was unknown. We found that two, and possibly all three, patients with impaired autoregulation had arterial spasm in the immediate preoperative period. In all other aspects, their preoperative clinical assessment was indistinguishable from those patients with intact autoregulation.

A number of studies have demonstrated that CBF is either focally or globally reduced in patients with arterial spasm, however, the clinical significance of these flow abnormalities remains unclear. In our patients, arterial spasm produced a 25% reduction in CBF preoperatively but had no effect on their clinical status, and all were classified neurologically as Grade I. In a larger series of 50 patients with SAH, we found several examples of clinically silent vasospasm producing severe reductions in CBF in patients who were neurologically well. Observations such as these have given rise to uncertainty concerning the significance of spasm. The results of the present study indicate that the secondary effect of arterial spasm, that of reducing cerebrovascular reserve, may be of greater clinical importance than the primary reduction in CBF. Arterial constriction causes an increase in arterial resistance, thus tending to reduce CBF. The cerebral arterioles will then dilate in an attempt to balance the increase in arterial resistance with a compensatory decrease in arteriolar resistance. This concept has been validated experimentally by Grubb, et al., who showed that cerebral blood volume was increased by 58% in patients with severe vasospasm, indicating a massive dilatation of the intraparenchymal arterioles. Although this will minimize reductions in CBF, it will also reduce the extent to which the arterioles can respond to a superimposed dilatory stimulus.

Evidence of a depleted vascular reserve was present throughout the clinical course of our patients with arterial spasm. Preoperatively, CBF was reduced when compared to patients without spasm. Intraoperatively, they were found to have impaired autoregulation. Substantial reductions in CBF occurred during induced hypotension, and CBF remained depressed when MABP was returned to normal. The postoperative period. It is clear from our results that arterial spasm may be of greater clinical importance than the primary reduction in CBF. Arterial constriction causes an increase in arterial resistance, thus tending to reduce CBF. The cerebral arterioles will then dilate in an attempt to balance the increase in arterial resistance with a compensatory decrease in arteriolar resistance. This concept has been validated experimentally by Grubb, et al., who showed that cerebral blood volume was increased by 58% in patients with severe vasospasm, indicating a massive dilatation of the intraparenchymal arterioles. Although this will minimize reductions in CBF, it will also reduce the extent to which the arterioles can respond to a superimposed dilatory stimulus.

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was the cause of the postoperative Wg abnormalities. It is also possible that these abnormalities were the result of mechanical damage or that the effects were less pronounced in Group I patients due to the development of reactive hyperemia. Since there were no associated neurological abnormalities, the clinical significance of these flow disturbances remains uncertain.

There are several factors that may have contributed to the observed protection from ischemia. Both halothane$^{15,17}$ and enflurane$^{16}$ are known to depress cerebral metabolism and, therefore, will reduce cerebral oxygen requirements. In addition, these agents have a direct vasodilating effect on the cerebral vasculature which increases with increasing concentration.$^{15,16,26}$ We found that under normotensive halothane anesthesia, Fg was increased by 28% in Group I patients and by 18% in Group II patients when compared to preoperative flow values. The increases in CBF noted during hypotension would support the vasodilating influence of increasing concentrations of halothane. Clearly, the combined effect of reduced oxygen requirements and enhanced CBF will help to prevent tissue hypoxia. The use of mannitol may also have contributed to the protection from ischemia. Mannitol, together with CSF drainage, "shrinks" the brain, thus reducing the pressure required for retraction. Mannitol is also known to reduce edema and to increase blood flow in areas of acute ischemia.$^{10,14}$ The final protective factor is the relatively short duration of the flow reductions. Several studies have shown that both the mortality and morbidity associated with cerebral ischemia are related not only to the degree of ischemia but also to its duration.$^{7,17,18}$ Moranetz, et al.,$^{18}$ found that 2 to 3 hours of ischemia was well tolerated in unanesthetized monkeys, providing CBF remained above 12 ml/100 gm/min. Increased tolerance would be expected if cerebral metabolism were depressed. When the above conditions are combined, it would appear that relatively severe reductions in CBF (to as low as 20 ml/100 gm/min in the unretracted hemisphere) are well tolerated for brief periods. This observation is supported by previous clinical studies from this center reporting good results achieved when using profound hypotension during aneurysm surgery.$^{1,3,5}$

Summary

We found that in the majority of Grade I patients, CBF remained above 30 ml/100 gm/min during profound hypotension at MABP of 40 mm Hg. Those patients in whom CBF fell below 30 ml/100 gm/min were protected from cerebral ischemia, probably through the combined effects of halothane (or enflurane), mannitol, and the relatively short duration of the flow reductions. Postoperatively, there was evidence of trauma at the site of retraction, and this was most pronounced in those patients with a low intraoperative CBF and no postoperative reactive hyperemia. There were no associated neurological abnormalities. We have suggested that the major clinical significance of arterial spasm is the resultant hemodynamic instability. Although these patients were protected from ischemic damage during surgical hypotension, autoregulatory impairment persisted well into the postoperative period and the patients were susceptible to ischemic deficits of late onset when subjected to a superimposed hemodynamic stress. Characteristic CBF abnormalities were identified at all three stages of their clinical management: preoperatively, intraoperatively, and postoperatively.

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