Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms

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The operative management of large and giant aneurysms is complicated by their typically atheromatous and thick walls, frequent intramural thrombosis with calcification, and broad-based necks that often incorporate perforating and other vital vessels. Not infrequently, it is necessary to at least focally arrest the intracranial circulation and open or excise these aneurysms to facilitate vascular reconstruction. This maneuver, in patients whose disease processes have destroyed autoregulatory function or who have inadequate sources of anatomical collateral supply, may cause the threshold for permanent ischemic injury to be exceeded. The authors have recently treated 14 such patients while under electroencephalographic monitoring to document electrical burst suppression induced by the administration of etomidate, followed by temporary clipping to permit vascular repair and intraoperative angiography to document patency of parent arteries. Up to 60 minutes of internal carotid artery occlusion, 35 minutes of middle cerebral artery occlusion, 19 minutes of upper basilar artery occlusion, and 4.89 minutes of lower basilar artery occlusion have been well tolerated using this protocol. In such situations, etomidate may be effective in protecting the cerebral circulation without the detrimental cardiotoxicity observed with protective doses of barbiturates.

The widespread adoption of modern microsurgical methods employing a myriad of available clip types and sizes has largely solved the technical problems associated with small cerebral aneurysms. The ideal therapeutic result (that is, obliteration of the aneurysm with preservation of afferent and efferent arteries and perforating vessels) is much more difficult to achieve with some large aneurysms (12 to 25 mm in greatest diameter) and with many giant aneurysms (> 25 mm). Thick, atheromatous, and calcific walls, intramural thrombosis, and broad-based necks that incorporate small perforating arteries and even parent vessels can make direct clipping impossible without temporary interruption of the cerebral circulation. The duration of temporary arterial occlusion for such vascular reconstruction can exceed the ischemic tolerance of brain tissue, especially if the patient's condition is complicated by recent subarachnoid hemorrhage (SAH) with loss of autoregulatory capacity.

Barbiturates have been shown to protect the brain in a number of animal models of hypoxia and ischemia; however, the cardiac effects frequently encountered at the dosage required can depress mean blood pressure sufficiently to jeopardize collateral flow during temporary occlusion. 24'25 The unique properties of etomidate,* which produces marked depression of cerebral metabolism with minimal cardiac toxicity, led us to try this agent for protecting the cerebral circulation during temporary vascular occlusion in the treatment of difficult large and giant aneurysms.24'25

Clinical Material and Methods

Patient Population

Over the past 13 months, 14 patients were treated at the University of Texas Health Science Center at Dallas for difficult large and giant intracranial aneurysms. In these cases, the radiographic studies suggested that sim-
ple direct clipping of the lesion would not be possible. As shown in Table 1, four patients were found to have proximal paraclinoidal aneurysms, one patient had a giant aneurysm of the middle cerebral artery bifurcation, seven patients had distal basilar artery aneurysms, and two patients had lesions in the region of the vertebral confluens, one of which was fusiform and involved most of the lower basilar trunk. Six patients were referred to this institution within 2 weeks after SAH, and eight patients were initially evaluated for mass lesions with symptoms of local mass effect (six cases) or elevated intracranial pressure (two cases). The nine women and five men ranged in age between 28 and 75 years (mean 55 years). The average age of those patients presenting with symptoms of mass effect was 57 years and of those with hemorrhage was 53 years.

Three patients had undergone prior neurosurgical procedures. One patient (Case 3), whose proximal carotid artery aneurysm had produced progressive loss of vision, underwent surgical exploration and unsuccessful treatment elsewhere 2 weeks before being operated on at our center. The second patient (Case 11) had undergone craniotomy at another institution 7 years before his present admission for treatment of a basilar bifurcation aneurysm. The lesion ruptured intraoperatively and was encased in methyl methacrylate and not clipped. He was referred to this center following a second SAH. The third patient (Case 14) underwent internal carotid artery ligation 9 years before her latest admission for a symptomatic giant aneurysm of the right cavernous carotid artery. The verteobasilar circulation was recruited for supply of the right middle cerebral territory, and she subsequently developed a giant fusiform aneurysm of the proximal basilar artery.

### Surgical Treatment and Methods

Regardless of whether SAH had occurred, all patients were premedicated with therapeutic levels of appropriate anticonvulsant drugs and steroids. Normovolemia or modest hypervolemia was achieved with preoperative colloid and crystalloid infusion targeting a central venous pressure of 6 to 10 cm H2O or a pulmonary capillary wedge pressure of 10 to 18 mm Hg. Swan-Ganz catheters were placed in patients whose general medical condition or cardiac disease placed them at high perioperative risk.

The patients were positioned for the surgical approach, and appropriate scalp sites were prepared with acetone and an abrasive gel for electrode placement. A reference lead was placed just superior to the nasion, an inferior frontal lead was placed superior to the brow, and a mastoid electrode was placed posteriorly to permit monitoring of hemispheric cortical activity. In general, bilateral hemispheric monitoring was used. When this was not possible due to patient positioning or planned scalp incisions, a single hemisphere was monitored. Following electrode placement, acceptable impedance was confirmed. On occasion, the surgical preparation and draping caused malfunction of the electrodes; this was usually due to seepage of antiseptic solution. This malfunction was detected by changes in impedance and was corrected by replacing the faulty electrode prior to skin incision. Cerebral activity was monitored with a Life Scan electroencephalograph.† The Life Scan system contains a self-test mode with automatic 100-μV 1-Hz calibration upon unit activation. A 400-μV amplitude was chosen on a 5-minute time base.

General endotracheal anesthesia was induced with thiopental, sufentanil, and vecuronium bromide, and was maintained with intermittent sufentanil bolus, isoflurane, and 50% nitrous oxide in oxygen. Ventilation

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*Abbreviations: AICA = anterior inferior cerebellar artery; ICA = internal carotid artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; SCA = superior cerebellar artery. The SAH grading was based on the classification of Hunt and Hess.

### TABLE 1

Clinical summary in 14 patients with difficult aneurysms of 12 mm or larger*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Presentation</th>
<th>Site of Aneurysm</th>
<th>Site of Occlusion</th>
<th>Duration of Occlusion (min)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>mass effect</td>
<td>paraclinoidal</td>
<td>cervical ICA</td>
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<td>cervical ICA</td>
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<td>4</td>
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<td>5</td>
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<td>MCA</td>
<td>MCA</td>
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<td>6</td>
<td>50</td>
<td>SAH Grade III, Day 4</td>
<td>basilar bifurcation</td>
<td>upper basilar, above SCA</td>
<td>17</td>
<td>poor</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>mass effect</td>
<td>basilar bifurcation</td>
<td>upper basilar, above SCA</td>
<td>20</td>
<td>poor</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>mass effect</td>
<td>basilar, SCA</td>
<td>upper basilar, below SCA</td>
<td>14</td>
<td>good</td>
</tr>
<tr>
<td>9</td>
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<tr>
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<td>19</td>
<td>good</td>
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<tr>
<td>12</td>
<td>68</td>
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<td>basilar bifurcation</td>
<td>upper basilar, below SCA</td>
<td>24</td>
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<td>28</td>
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<tr>
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<td>41</td>
<td>mass effect</td>
<td>basilar trunk, fusiform</td>
<td>lower basilar</td>
<td>61</td>
<td>poor</td>
</tr>
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</table>

†Life Scan electroencephalograph manufactured by Neurometrics, Diatek Corp., San Diego, California.
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FIG. 1. Radiographic findings in Case 4. **Upper Left:** Preoperative enhanced computerized tomography scans demonstrating a giant aneurysm projecting from the left carotid cistern. **Lower Left:** Preoperative left carotid angiogram, anteroposterior view, suggesting nearly complete thrombosis of the aneurysm. **Right:** Postoperative left carotid angiogram, anteroposterior view, following clipping and resection of the aneurysm.

was controlled, and PaCO₂ was maintained at 25 to 28 mm Hg.

In patients harboring proximal carotid artery aneurysms, the cervical internal carotid artery was exposed prior to opening the scalp for both proximal control and access for intraoperative angiography. Routine pterional exposure was then used for dissection of the distal internal carotid artery and the aneurysm, and resection of the anterior clinoid process when required before applying temporary clips. In Case 4, the massive size of the aneurysm prevented subarachnoid exposure prior to partial frontal lobectomy (Fig. 1). The patient with a giant aneurysm involving the middle cerebral artery bifurcation (Case 5) also required partial temporal lobectomy before dissection of her sylvian fissure (Figs. 2 and 3). Wide exposure was then obtained of the M₁ segment and each M₂ branch of the middle cerebral artery and of the lateral lenticulostriate arteries.

Each patient with a distal basilar artery aneurysm was positioned for a pterional transsylvian exposure of the interpeduncular cistern. Scalp electrode placement was identical to that in the patients with carotid and middle cerebral artery aneurysms. Sharp subarachnoid dissection was used to expose the distal basilar trunk for temporary clip placement either above or below the origins of the superior cerebellar arteries. In each case, the P₁ segments of the posterior cerebral artery were isolated just proximal to the P₁–P₂ junction, although temporary trapping was not required because satisfactory softening of the aneurysm was obtained with proximal occlusion.

The two patients with vertebral confluens aneurysms (Cases 13 and 14) were placed in the lateral position. Electroencephalographic (EEG) monitoring of the contralateral hemisphere was achieved; in Case 13, a lateral retromastoid craniectomy including the foramen magnum gave adequate exposure (Fig. 4). In Case 14, an additional supratentorial temporal craniotomy with sacrifice of the transverse sinus was used to yield distal control of the basilar artery via a subtemporal transventricular approach. In each case, proximal exposure of both vertebral arteries at the vertebral confluens was achieved by subarachnoid dissection with minimal brain-stem retraction.

After the dura was opened, the systolic blood pressure was maintained at 110 to 120 mm Hg. The afferent and efferent vessels were then dissected and the aneurysmal neck exposed, after which the systolic blood pressure was elevated to 120 to 130 mm Hg. Prior to temporary clip placement, nitrous oxide was replaced by 100% oxygen. The raw EEG data were observed as etomidate was administered intravenously. Etomidate dosage was titrated until eight to 10 screens of electrical silence appeared between bursts of activity. Burst suppression was typically achieved in less than 2 minutes, requiring a dose of 0.4 to 0.5 mg/kg. Further administration of etomidate in 0.1-mg/kg increments was given as the number of electrically silent screens de-
Etomidate in surgery for large and giant aneurysms

FIG. 2. Radiographic findings in Case 5. Left: Preoperative enhanced computerized tomography scan revealing a giant middle cerebral artery (MCA) aneurysm. Center: Preoperative right carotid arteriogram, lateral view, disclosing partial filling of the aneurysm and a pronounced temporal mass effect. Right: Postoperative right carotid angiogram, lateral view, documenting patency of the MCA branches.

FIG. 3. Schematic drawings of the surgical procedure in Case 5 showing temporary clipping and opening of the aneurysm (left), followed by evacuation of the aneurysmal contents and resection leaving a clippable cuff of tissue (right).

FIG. 4. Right vertebral angiograms, anteroposterior view, in Case 13. Left: Preoperative study revealing a partially thrombosed aneurysm at the vertebral confluens. Right: Immediate postoperative study showing mild stenosis of the lower basilar trunk.

Etomidate was administered in a dose of 0.2 to 0.3 mg/kg to a maximum of four or five. This dosage of etomidate resulted in a maximum of 5% reduction in blood pressure. After satisfactory burst suppression was documented, temporary arterial clips were placed. Following temporary clip removal, etomidate was discontinued and the anesthetic level was maintained with isoflurane, 50% nitrous oxide in oxygen, and muscle relaxation.

Following patient positioning for proximal carotid artery aneurysm exposure, an operative microscope with a portable C-arm and a 6-in. image intensifier was manipulated until an appropriate oblique view was obtained without obstruction by the Mayfield-Kees head-holder. After aneurysm clipping, a No. 16 Angiocath was inserted into the previously exposed cervical internal carotid artery for injection of contrast medium. Fluoroscopic radiographs were obtained with a frame rate of approximately 4/sec using a manual triggering device. The images were stored on a video storage device for subsequent review and hard-film copying. Patients with giant middle cerebral and vertebrobasilar artery aneurysms were taken to the angiography suite while still under general anesthesia for definitive angiography to insure patency of major vessels.

Surgical Results

As shown in Table 1, 10 of the 14 patients treated as described had a good outcome. These patients either are neurologically normal or have mild deficits that do not preclude a return to their previous occupation or
lifestyle. Three patients were considered to have poor outcome at 3 to 7 months after treatment; they had either dense focal neurological deficits or alterations in consciousness that precluded an independent life. One patient (Case 10) died. She was a 75-year-old woman with severe congestive heart failure who was lethargic and hemiparetic after SAH from a posteriorly projecting basilar bifurcation aneurysm. Her operative procedure was complicated by intraoperative hemorrhage requiring 11 minutes of temporary occlusion, and a clip was applied in a blood-filled field. She awakened hemiplegic and died 2 weeks later. At autopsy, the clip was noted to have occluded a leash of perforating arteries, resulting in midbrain infarction.

Although this is an admittedly diverse population, we believe that the outcome of these patients was not closely related to the duration of occlusion, but rather to other complications of SAH or conceptual or technical flaws in their management. One patient (Case 6) had an excellent recovery following 17 minutes of upper basilar artery occlusion, but required 3 weeks of hypervolemic and hypertensive therapy for delayed ischemic symptoms due to vasospasm. Despite an immediate postoperative angiogram showing successful clipping of the aneurysm, a study 4 weeks later revealed the formation of a new aneurysm proximal to the clip, presumably due to iatrogenic hypertension. The patient underwent repeat subtemporal surgery, and significant peduncular retraction was necessary to secure the second aneurysm. He has remained hemiplegic since this procedure. Another patient (Case 7) tolerated 20 minutes of upper basilar artery occlusion, but cardiac and pulmonary complications related to her age contributed to a long course of respiratory dependency from which she is improving.

Due to the diversity in anatomy and presenting symptoms in a series such as this, it would be quite difficult to prospectively randomize therapy to determine if etomidate was altering the expected tolerance of each patient under the effect of general anesthetic. We have been impressed, however, with the actual duration of occlusion which was tolerated well, including 60 minutes for the internal carotid artery, 35 minutes for the middle cerebral artery, 19 minutes for the upper basilar artery, and 61 minutes of basilar trunk trapping with recovery of level of alertness. Of particular note is the relative paucity of side effects, the maintenance of normotension, and the lack of prolongation of anesthetic effect associated with etomidate at the dosage used.

**Discussion**

The use of Hunterian ligation procedures in the management of giant intracranial aneurysms remains fraught with hazard. Data from the Cooperative Study demonstrated ischemic complications in 49% of cases following internal carotid artery ligation and in 28% of cases following common carotid artery ligation. These data are supported by the series of Kak, et al., published in 1973. Significant morbidity has also attended vertebral and basilar artery ligation for posterior circu-

lative aneurysms. The report of Pelz, et al., on 71 patients treated in this manner demonstrated that only two-thirds of cases had a favorable outcome. In a review of reported cases, Roski and Spetzler noted that 86% of aneurysms treated by carotid artery ligation were found postoperatively to be either reduced in size or not visualized; however, progressive enlargement of aneurysms has been described following carotid artery ligation, and rebleeding episodes occur in roughly 8% of cases so treated.

Initial data suggested that the extracranial-intracranial (EC-IC) bypass procedure might substantially reduce ischemic risk following proximal ligation procedures. Other authors have reported less favorable protection, and this is consistent with our experience. Heros has implicated embolic phenomena in cases in which carotid artery ligation and EC-IC bypass procedures failed. In addition, angiographic reflow and aneurysm rupture has been documented following proximal ligation and bypass surgery.

Direct surgical treatment with the attendant salvage of afferent and efferent vessels and decompression of adjacent brain tissue, cranial nerves, or blood vessels constitutes the primary goal of interventional care at our center. A number of technical developments have made this goal more often obtainable than was previously possible. Sugita, et al., developed a series of clips up to 40 mm in length with closing strengths which reach 1100 gm near the proximal aspect of the blades. A plethora of shapes and sizes of fenestrated clips are now available which permit creative reconstruction of parent arteries. Sundt's booster clip has expanded the principle of tandem and piggyback clipping to add closing strength to innovative clip arrangements. Nevertheless, we have routinely found it necessary either to temporarily trap or to proximally occlude most giant aneurysms, occasionally using suction decompression to soften the neck adequately for clip placement. While hypothermia and cardiac arrest have been used effectively with ischemic tolerance, we have relied on local circulatory occlusion and pharmacological protection.

For the last several years we have used thiopental to protect the cerebral circulation. Despite maintenance of normovolemia, however, the cardiac depressant effects at the required dosage were worrisome and jeopardized collateral supply to the ischemic territory. In addition, patients who had undergone protracted procedures with episodes of temporary occlusion were extremely slow to awaken and often required overnight ventilatory support. The known pharmacological properties of etomidate stimulated our trial of this agent over the past 13 months. The chemical composition of etomidate is R(+)1-(a-methylbenzyl)imidazole-5-carboxylate, which is unrelated to that of any other intravenous anesthetic. After an induction dose of etomidate, a rapid loss of consciousness ensues. The duration of its central nervous system effects is dose-dependent,
but after a typical induction dose of 0.3 mg/kg, the patient regains consciousness within 3 to 5 minutes. The short duration of action appears to be secondary to tissue redistribution.

Etomidate produces EEG effects similar to those achieved with thiopental. Changes in the EEG pattern following etomidate injection have been characterized by Ghoneim and Yamada into four stages. Initial changes consist of an increase in alpha wave amplitude with a mixture of theta burst. Progressive EEG changes culminate in a periodic burst-suppression pattern. Milde, et al., demonstrated a progressive decrease in electrical activity with constant etomidate infusion in dogs, and Kugler, et al., documented a transient isoelectric EEG pattern following a single induction dose of 0.2 mg/kg in humans.

Cerebral metabolic energy expenditures are divided between generation of electrical impulses and maintenance of cellular ionic gradients. Anesthetic agents have been shown to produce cerebral metabolic suppression due to decreased neuronal activity. Etomidate suppresses electrical activity in a dose-related fashion, progressing to burst suppression and finally to electrical silence. Burst suppression is characterized by isoelectric intervals interrupted by bursts of activity at 8 to 12 Hz which diminish to 1 to 4 Hz prior to electrical silence. In canine experiments, etomidate infusions have been shown to decrease the cerebral metabolic rate of oxygen (CMRO2) until an isoelectric EEG pattern is obtained. Once this level of neuronal depression was achieved, the CMRO2 stabilized at 48% of control levels. Further loading with etomidate was ineffective in depressing the CMRO2 beyond this point.

Etomidate has been shown to be a potent cellular metabolic depressant and to decrease cerebral blood flow (CBF) in humans. Decreases in CBF are probably due to decreases in CMRO2 as well as being a direct effect of etomidate on the cerebral vessels. Following etomidate infusion in the dog, the adenosine triphosphate and phosphocreatine levels and the energy charge remained normal, suggesting adequate CBF for any given CMRO2. Etomidate has been shown to prolong survival times following experimental hypoxic and ischemic insults in animals. Even with massive doses in dogs, etomidate has demonstrated very little cardiovascular depression.

Previously described potential adverse side effects of this drug were not seen in this series. Increased epileptiform activity in epileptic patients was noted by Ebrahim, et al. All patients in this series were given anticonvulsant drugs prior to surgery and no epileptiform discharges were noted intraoperatively. Of perhaps more concern for patients given protracted doses of this agent is the reported inhibition of steroid synthesis. In vitro studies have demonstrated a block in cortisol production occurring at levels of etomidate likely to be used intraoperatively. Patients undergoing abdominal hysterectomy were found to have depressed cortisol and aldosterone secretion levels for 8 to 22 hours following surgery. We have routinely weaned patients from steroids slowly over 5 to 7 days to prevent this potential complication.

Conclusions

The results of our early experience with etomidate suggest both that it has significant potential value as a protective agent during iatrogenic cerebral ischemia and that its administration can be safely and systemically titrated with intraoperative EEG monitoring. The available experimental data demonstrate that the CMRO2 is significantly affected by doses of this magnitude, and animal studies as well as this clinical experience support the safety of this regimen. It is our impression that the cardiovascular depression associated with etomidate is substantially less severe than that observed with high doses of barbiturates and that postoperative recovery of consciousness is much quicker, allowing earlier neurological assessment. The development of this therapeutic protocol involving cerebral metabolic depression, neurophysiological monitoring, temporary local circulatory arrest, vascular reconstruction, and early angiography has permitted direct obliteration of certain difficult aneurysms with preservation of normal cerebrovascular anatomy.

Acknowledgment

The authors extend sincere thanks to Mrs. Wilma Scheppe for her skilled help in preparation of this manuscript.

References


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