Ischemic Brain Rescue by Transvenous Perfusion in Baboons With Venous Sinus Occlusion

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We studied brain retroperfusion in nine adult baboons. Experiments in four baboons determined techniques and the safety of retroperfusion, and experiments in three baboons determined the ability of retroperfusion to reverse cerebral ischemia. Two baboons died before retroperfusion. Arterial blood was continuously circulated by an external pumping system from one femoral artery into the intracranial sinuses through specially designed balloon-tipped catheters placed percutaneously into the sigmoid sinuses bilaterally. The balloons intermittently occluded the sinuses. Ischemia was produced by occluding the left middle cerebral artery. Standard and computed electroencephalography with topographic mapping monitored the onset and reversal of ischemia. Retroperfusion rate exceeded 50 ml/min with a mean intrasinus pressure increase of 27 (0-149) mm Hg in all seven experiments. Venograms demonstrated complete or partial filling of the superior sagittal sinus in each experiment. Four experiments without ischemia established maximal balloon occlusion cycles, retroperfusion rates, and sinus pressure changes. These four baboons were neurologically normal after retroperfusion; two had normal magnetic resonance imaging scans. Ischemic changes, detected by electroencephalography following middle cerebral artery occlusion, were reversed with retroperfusion in all three ischemia experiments. Autopsies in the seven baboons demonstrated no parenchymal hemorrhage or edema. Our results suggest that further investigation of retroperfusion, and possibly retroinfusion of agents for cerebral protection, is warranted. (Stroke 1990;21:87-93)

Stroke afflicts 500,000 Americans yearly. Research has failed to reduce stroke morbidity substantially while the cost of stroke rehabilitation has climbed steadily, reaching 3 billion dollars yearly.

Acute surgical intervention for stroke has not been possible in most instances. Anticoagulation for completed stroke is of no proven value, and there is limited evidence of its benefit for stroke in progress. There is hope for intra-arterial thrombolytic agents such as urokinase or tissue plasminogen activators, but they carry risks of cerebral hemorrhage and are still unproven.

Common to all of these treatments is the substantial time needed to reverse ischemia. A technique that could be initiated within a few hours after ischemic symptom onset and that could support brain tissue until surgical or medical treatment was completed would be very desirable. Reports of a new technique for the reversal of myocardial ischemia using arterial blood pumped retrogradely into the coronary sinus (coronary venous retroperfusion) have suggested that it is safe and effective. We have adapted this technique for the rescue of ischemic brain.

The concept of perfusing the brain through the venous system is unconventional and has raised concerns about possible deleterious effects such as elevated intracranial pressure, subarachnoid hemorrhage, and brain edema. It has also raised doubts as to the feasibility of promptly catheterizing intracranial veins and the ability to perfuse a capillary bed in a retrograde manner, with adequate volume to sustain brain function during ischemia. We report the results of preliminary studies to determine the safety and efficacy of brain retroperfusion.
Materials and Methods

Nine experiments were attempted in adult baboons (Papio anubis) of either sex weighing 15–25 kg, four experiments to determine the feasibility of retroperfusion and its possible side effects and five experiments to determine retroperfusion’s ability to reverse short-term cerebral ischemia. Baboons for both types of experiments were prepared the same, except that a snare around the right middle cerebral artery (MCA) provided cerebral ischemia.

All nine baboons were preanesthetized with 10 mg/kg i.m. ketamine and 0.4 mg i.m. atropine and intravenously anesthetized for intubation with 5–10 mg/kg thiopental sodium. The baboons were placed on 0.5–1.5% halothane inhalation anesthesia using a Bird respiratory (Bird Respirator Co., Riverside, California). Blood pressure, electrocardiogram, expired CO₂ concentration, and O₂ saturation were continuously monitored. Pancuronium bromide (0.1 mg/kg repeated every 2 hours) and heparin (2,000 units repeated every 2 hours) were given intravenously.

Four days before all ischemia experiments, a snare was surgically placed around the proximal right MCA. At the time of experimental preparation, the distal end of the snare was retrieved from its subcutaneous burial site and used to reversibly occlude the left MCA. In one experiment, ischemia was also produced in the right MCA territory by superselective catheterization and embolization with 2x4-mm Gel-foam sponge particles (The Upjohn Co., Kalamazoo, Michigan).

The electroencephalogram (EEG) was recorded with 28 needle electrodes placed according to the 10-20 international system, with extra placements interpolated. All 28 channels were recorded on optical disks (Brain Imager, Neuroscience, Inc., Milpitas, California).

A 50% change in amplitude of any frequency band (delta, theta, alpha, or beta) compared with the baseline amplitude after MCA occlusion in one or both hemispheres was considered to be evidence for an EEG change consistent with ischemic dysfunction of the brain underlying the recording electrodes. Return of the EEG amplitude to baseline levels was thought to be evidence of improvement in cerebral blood flow. The correlation of EEG changes with the onset and reversal of ischemia has been reported for both humans and animals.

The retroperfusion catheters (Retroperfusion Systems Inc., Costa Mesa, California) were made of a specially formulated thermoplastic material and were 100 cm long. The triple-lumen catheters permitted retroperfusion of arterial blood, monitoring of venous sinus pressure, and pulsed-air inflation of a balloon (10 mm wide x 15 mm long) at the distal end of the catheter.

Under fluoroscopic control, both jugular bulbs were catheterized. Proper position was documented by hand-injection of 3–5 ml nonionic contrast material (iopamidol, Squibb Diagnostics, New Brunswick, New Jersey). The extent of filling of the cerebral venous structures (straight sinus, internal cerebral veins, torcula, superior sagittal sinus, and cortical veins) was carefully noted. The catheters were connected to a specially designed pumping system (Retroperfusion Systems Inc.) that concomitantly produced cyclic inflation of the balloons (8 seconds inflated, 2 seconds deflated) while continuously infusing through one or both catheters arterial blood harvested from the femoral arterial line at a rate varying between 5 and 245 ml/min (Figure 1). Magnetic resonance imaging (MRI) was performed 3 days after retroperfusion in two baboons without MCA occlusion.

Upon completion of each experiment, the baboon was killed with thiopental sodium (15 mg/kg i.v.) and potassium chloride (3 meq/kg i.v.). The brain was removed, inspected, cut into 1-cm-thick coronal slices, and grossly inspected for hemorrhage and edema.

Results

Nine experiments were attempted. There were two brain deaths due to the anesthetic (halothane-induced hypotension) before either ischemia or retroperfusion. Experiments in four baboons studied the safety of retroperfusion, and experiments in three

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**Figure 1.** Diagram of experimental setup in baboons, showing venous sinus and femoral artery catheter placement and retroperfusion pump connecting these catheters.
studied the ability of retroperfusion to reverse cerebral ischemia.

In all nine experiments attempted, it was possible to catheterize both jugular bulbs and to satisfactorily position the retroperfusion catheters using either the direct jugular approach (in five baboons) or the transfemoral approach (in the other four). The latter approach eliminated the need for a jugular vein cut-down and reduced the average resting intrasinus pressures associated with bilateral proximal internal jugular occlusions from 11.4 to 8.0 mm Hg. The average time needed to position a balloon-tipped, triple-lumen catheter in the sigmoid sinus of these small animals was 34 minutes. Catheters could be placed in as little as 2 minutes.

In all seven baboons that were retroperfused, venograms with or without inflated balloons demonstrated filling of the cerebral venous vasculature ranging from the caudal superior sagittal sinus (in five) to the cephalad superior sagittal sinus, straight sinus, internal cerebral veins, and cortical veins (in four) (Figure 2).

Because the retroperfusion catheters partially occluded the jugular bulb, drainage of the cerebral vasculature occurred through alternate pathways using emissary veins, the suboccipital plexus, scalp veins, or the cavernous sinus (superior ophthalmic vein, pterygoid plexus, and inferior petrosal sinus). It was not possible in baboons with MCA occlusion to opacify the cerebral arteries in a retrograde manner, even in the ischemic territory.

Maximum retroperfusion rates from all seven completed experiments varied between 50 and 245 (average 120) ml/min. A large portion of this flow passed into the external jugular system and did not reach the cerebral tissue. Maximum intracerebral venous pressure during all seven completed experiments varied between 16 and 176 (average 54.8) mm Hg, with a maximum increase from baseline varying between 0 and 149 (average 26.6) mm Hg. Intracerebral pressures of >70 mm Hg were regularly accompanied by a deterioration in the EEG.

Ischemia was reversibly produced a minimum of four and a maximum of 20 times in three baboons. Common carotid angiograms confirmed occlusion of the right MCA just before and during retroperfusion.

Retroperfusion during eight episodes of ischemia increased venous blood pressure by an average of 9 mm Hg, to 21 mm Hg (Table 1), with the retroperfusion rate averaging 94 ml/min.

Superselective catheterization of the distal intracranial internal carotid artery was successful in a single baboon. Embolization with 2x4 mm Gelfoam sponge particles through this catheter produced ischemia in the right MCA territory, eliminating the need
for neurosurgical placement of a snare in future experiments.

Ischemia before the start of retroperfusion lasted between 0.5 and 16.1 (average 4.15) minutes. EEG evidence of ischemia was apparent within as little as 0.25 minutes after MCA occlusion. Retroperfusion returned the EEG to baseline within 0.25-18.0 (average 5.0) minutes. There was little change from the baseline blood pressure during either ischemia or retroperfusion (Table 1). Retroperfusion in each ischemic experiment was started and stopped 1-5 (a total of 8) times. In each instance there was EEG evidence that ischemia was reversed with retroperfusion and returned when retroperfusion was stopped (Figure 3).

Following MCA occlusion in two baboons, computed EEG changes were characterized by a relative increase in delta activity as a result of suppression of alpha and beta activity. In the third baboon, ischemic changes consisted of ipsilateral suppression of alpha activity with relative preservation of slow rhythms. After the opening of the MCA snares, EEG activity returned to baseline in all three baboons.

Each episode of retroperfusion lasted between 2.0 and 29.1 (average 12.4) minutes. Excluded from the average was the longest period of retroperfusion (430 minutes at a rate of 122 ml/min). During this period, normal EEG was sustained for 180 minutes in the face of MCA occlusion. At that point the EEG began to deteriorate, and at 420 minutes the EEG showed changes consistent with severe MCA territory injury.

MRI scans obtained 3 days after retroperfusion in two baboons were normal. Examination of brain sections from all seven baboons revealed no evidence of subarachnoid or deep hemorrhage or of edema. The brains were not examined microscopically.

Discussion

The effective preservation of ischemic brain tissue remains an elusive goal. There has been historical interest in the use of the cerebral venous system to nourish ischemic brain. Surgical attempts to anastomose the common carotid artery and external jugular vein in hopes of providing arterial blood to the brain were reported as early as 1896 but were unsuccessful.13-16

Following air embolism, blood has been pumped retrogradely via the superior vena cava into the brain to wash the emboli from the cerebral vessels.17,18 Results have ranged from immediate death to no neurologic sequelae.

Retroperfusion of arterial blood via the coronary sinus to salvage ischemic myocardium was first demonstrated in 1976 by Meerbaum et al19 and Farcot et al20 using dogs. In 1986, clinical retroperfusion studies were begun in patients experiencing unstable angina? and during percutaneous transluminal coronary angioplasty.8 In both reports, retroperfusion reduced the frequency of anginal episodes.

We proposed that this same retroperfusion technique could be adapted to salvage brain subjected to acute ischemia. Autologous arterial blood supplied through the cerebral veins during acute ischemia might provide temporary support to an ischemic area until normal perfusion could be restored. We developed a cerebral retroperfusion technique and tested its safety and effectiveness in a baboon model of MCA territory ischemia.

Our experiments show that it is possible to position retroperfusion catheters percutaneously from a femoral site at the outlet of the major sinuses draining the brain in a timely fashion. Application of this technique to humans appears feasible. One author’s experience with cerebral venous catheterization in cadavers and in patients with cerebral dural and pial arterial venous malformations has shown that venous sinus catheterization can be performed in 5 minutes.

Optimal retroperfusion rates are believed to be indicated by good filling of the cortical veins and venous sinuses, with venous blood pressures of <70 mm Hg. A protocol for finding the optimal pressure and flow limits of retroperfusion in each subject has been developed. Although we have not yet demonstrated filling of the capillary system, we surmise that at least some filling has occurred as ischemia (documented by EEG) was reversed in each of the three baboons in which this was attempted. Computed EEG techniques demonstrated the rapid onset of cerebral ischemia when the MCA was occluded and the resolution of this ischemia with retroperfusion. Repeatedly starting and stopping retroperfusion under ischemic conditions has firmly demonstrated that retroperfusion of arterial blood is directly correlated with this reversal in EEG abnormality.

To completely reverse EEG evidence of ischemia, the optimal retroperfusion rates were between 96 and 160 ml/min. Based on standard blood flow requirements for brain, retroperfusion alone equaled or exceeded each baboon’s total requirements. However, not all of this blood traveled to the brain. Venograms clearly showed that some retroperfused
FIGURE 3. Computed electroencephalographic (EEG) brain maps (above) with simultaneous raw EEG (below) in baboon with middle cerebral artery occlusion. Top left: baseline; top right: ischemia; bottom left: retroperfusion during occlusion; bottom right: ischemia, retroperfusion stopped.

Blood passed into the external venous system and never reached the brain. We do not know the volume of blood per minute that reached the brain or the ischemic bed during retroperfusion. Blood flow studies with microspheres have been designed to answer this question.
Previous authors have established that the EEG changes when cerebral blood flow falls to <20 ml/100 g brain tissue/min. It is important to note that EEG dysfunction is observed at cerebral blood flows that may be of insufficient quantity or duration to produce infarction in brain tissue. Thus, the EEG appears to be a monitor of dysfunction, but does not necessarily correlate with tissue infarction. Nevertheless, cortical infarction is not expected to occur under circumstances in which a continuously monitored EEG shows no significant change from baseline. Smaller subcortical infarctions can occur without changes in the surface EEG. The monitoring of somatosensory evoked potentials may provide information about these subcortical structures.

The safety of this procedure was suggested in all experiments by a lack of EEG deterioration, normal MRI scans (in two baboons), and the lack of hemorrhage or edema (in all seven baboons). Venous blood pressures of >70 mm Hg (secondary to high reperfusion rates) were accompanied by deterioration in the EEG, which returned to normal when retroperfusion was stopped. It is recognized that blood pressures measured at the tip of the retroperfusion catheter may not be representative of the pressures in small veins. However, when retroperfusion catheters were in their final positions, venous blood pressures appeared to correlate with subdural and intraparenchymal pressures.

Retroperfusion continued for up to 430 minutes without hemorrhage or edema. Retroperfusion (in one baboon) supported ischemic brain tissue for 180 minutes. EEG evidence of ischemia then appeared, despite continued retroperfusion.

Others have attempted retroperfusion with poor success. The success of our experiments appears to stem from our ability to control intrasinus pressure by intermittently deflating the balloons that obstructed the venous sinuses and to control the rate of continuous retroperfusion.

Many questions remain to be answered and will be the target of our next studies. Important considerations are retroperfusion’s ability to rescue brain after 1–4 hours of ischemia, a demonstration of retroperfusion of the ischemic capillary bed, and an identification of the time that ischemic brain can be supported by retroperfusion.

A strong consideration for future investigation has been given to retiroinfusion. This process of including pharmaceutical agents (such as a calcium channel blocker) within the retroperfusate (arterial blood) may increase the benefits of retroperfusion. This could be very important when retroperfusion is attempted after prolonged ischemia. Based on the experiments of others, we suspect that reversal of cerebral ischemia with preservation of some or all function may be possible when retroperfusion or retiroinfusion is initiated as late as 4 hours after the onset of an ischemic event. This obviously becomes of paramount importance if this technique is to be applied in the clinical setting in which patients experience an ischemic event outside a hospital. Based on our experience in the angiography suite, it would appear possible to institute retroperfusion <1 hour after a patient’s arrival in an emergency room. Clinical trials for such an event are now being designed.

Acknowledgments

We are greatly indebted to Miss Stephanie J. Smith for secretarial assistance and to Roy Jones, Lonnie Bivens, John Roberts, and Jerome Jackson for superb technical assistance.

References


**KEY WORDS** • cerebral ischemia • perfusion, venous • baboons
Ischemic brain rescue by transvenous perfusion in baboons with venous sinus occlusion.
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Stroke. 1990;21:87-93
doi: 10.1161/01.STR.21.1.87

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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