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Intracarotid Delivery of Drugs

The Potential and the Pitfalls

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The major efforts to selectively deliver drugs to the brain in the past decade have relied on smart molecular techniques to penetrate the blood–brain barrier, whereas intraarterial drug delivery has drawn relatively little attention. Meanwhile, rapid progress has been made in the field of endovascular surgery. Modern endovascular procedures can permit highly targeted drug delivery by the intracarotid route. Intracarotid drug delivery can be the primary route of drug delivery or it could be used to facilitate the delivery of smart neuropharmaceuticals. There have been few attempts to systematically understand the kinetics of intracarotid drugs. Anecdotal data suggest that intracarotid drug delivery is effective in the treatment of cerebral vasospasm, thromboembolic strokes, and neoplasms. Neuroanesthesiologists are frequently involved in the care of such high-risk patients. Therefore, it is necessary to understand the applications of intracarotid drug delivery and the unusual kinetics of intracarotid drugs.

FOR more than 50 yr, intracarotid anesthetic drugs have been used in diagnostic neuroradiology to locate brain functions.[1] In the 1980s, intracarotid drugs were extensively investigated for the treatment of malignant brain tumors.[2–6] However, the attempts at intracarotid chemotherapy of brain tumors proved disappointing because of unexplained neurotoxicity and a relatively modest impact on the clinical outcome of the disease.[7–9] Therefore, the enthusiasm for intracarotid drug delivery waned by the early 1990s. Intracarotid injections can rapidly generate high concentrations of drug within a region of interest at a fraction of the total systemic dose.[2,10] Consequently, intracarotid delivery can serve as the primary method of drug delivery, or the technique could be used to increase the effectiveness of other methods of brain-selective drug delivery that target specific characteristics of the blood–brain barrier (BBB).[11] Currently, intracarotid drugs are used for localizing neurologic functions in the brain and for the treatment of intractable cerebral vasospasm, ischemic strokes, and intracranial malignancies.[12]

In the past decade, rapid advances have been made in endovascular neurosurgery. These include the development of microcatheters and small balloon occluding catheters, which can be floated into distal regions of the brain. These devices can selectively deliver drugs or manipulate blood flows, in relatively small vascular territories consisting of 40–100 g of brain tissue.[13] The feasibility of intraarterial interventions on a limited scale decreases the risks of neurologic complications. Improved techniques of intraarterial delivery have also recently emerged that, compared with conventional infusions, can significantly augment tissue drug deposition.[14–16] Magnetic resonance imaging with temporal resolution sufficient to guide catheter placement, described as "interventional magnetic resonance imaging," is also rapidly advancing and could lead to novel intraarterial interventions guided by fast magnetic resonance imaging and spectroscopy.[17] Collectively, such technological advances compel us to reevaluate intracarotid drug delivery and ascertain its role in the current and future treatments of brain diseases.

An understanding of intracarotid drug delivery is important to anesthesiologists who are often involved in the care of patients receiving intracarotid drugs. This review rationalizes the use of intracarotid drugs and describes their present and future applications. It also discusses anesthetic management of the current therapeutic interventions using intracarotid drugs.

Anatomic Considerations

Some key anatomical features of the cerebral circulation affect intracarotid drug delivery to the brain. These include the size of the brain relative to the body weight, anatomical configuration of cerebral arteries, the state of the BBB, and the anatomical compartments within the brain.

The Size of the Brain Relative to the Body Weight Varies across Animal Species

In general, relative to body size, primates have a much larger brain weight than nonprimate animals, and even among primates, humans have a much greater brain-to-body weight ratio.[18] As a result, primates can tolerate greater intracarotid doses of drugs based on body weight. For example, an intracarotid

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dose of 8 mg/kg of an antineoplastic drug, carmustine, produces severe hemorrhaging necrotizing lesions in dogs, but the same dose is well tolerated in rhesus monkeys and in humans.[19–21]

The Configuration of Cerebral Arteries

Anatomical variations of the cerebral arteries can influence regional distribution and concentration of drugs after intracarotid delivery. The configuration of cerebral arteries varies (1) across animal species,[22] (2) within individuals of the same species, and (3) even in an individual over time.

The extent of communication between the external carotid artery and the internal carotid artery (ICA) greatly varies across animal species. Rabbits and primates show a clear separation of the intracranial and extracranial irrigations.[23–25] On the other hand, many animals, such as goats and pigs, have extensive collateral communications between the intracranial and extracranial arterial irrigations.[22] Even within animals of the same species, there can be significant differences in the origin and the size of the ICAs.[24] Smaller animals have larger external carotid arteries, and the sizes of the ICAs, relative to the vertebral arteries, differ across species. Therefore, ICA occlusion is fairly well tolerated in rodents and causes a transient decrease in blood flow in rabbits.[26] However, ICA occlusion often causes neurologic symptoms in humans.[27,28] The ability of human subjects to tolerate ICA occlusion depends largely on the configuration of the circle of Willis. Only 18% of human subjects have a balanced, symmetrical circle of Willis (fig. 1); therefore, there is a need to clinically test whether a patient can tolerate ICA occlusion before ICA sacrifice.[29–31] The configuration of the circle of Willis also determines the resistance of each arterial segment that could influence the distribution of intracarotid drugs.[32]

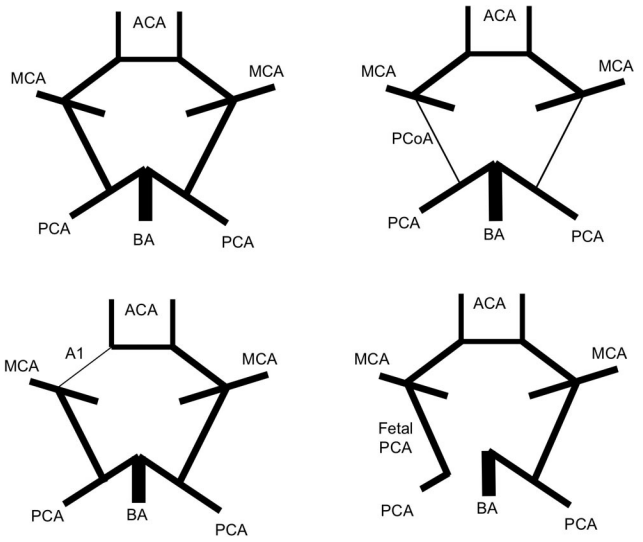

Fig. 1. Some variations in the anatomy of the circle of Willis in human subjects. A complete balanced circle is seen in 18% of the general population. Hypoplastic segment of the posterior cerebral artery (PCoA) is seen in 22%. Hypoplastic segment of the anterior cerebral artery (A1) is seen in 25%. A fetal posterior cerebral artery (fetal PCA) with hypoplastic posterior cerebral artery is seen in 15%.[29] ACA = anterior cerebral artery; BA = basilar artery; MCA = middle cerebral artery; PCA = posterior cerebral artery. From Duong *et al.*[29]; used with permission.

Furthermore, the blood flow in a given artery can change with time, which could affect the regional tissue concentrations of intracarotid drugs. It has been shown that the pharmacologic effects of intracarotid drugs, such as anesthetics, are directly related to cerebral blood flow (CBF).[33,34] If changes in blood flow have a significant effect on tissue drug concentrations, the arterial concentrations generated after injection of the same dose of a drug might be different over time even in the same individual. Consider, for example, superselective intracarotid infusion of papaverine for cerebral vasospasm. Initially, when blood flow is low, the concentration of the drug is high because of minimal dilution with arterial blood. As vasospasm resolves, blood flow increases and arterial concentration declines because of greater dilution.[35] In theory, the vasodilatory effects of intracarotid drugs that augment local blood flow may paradoxically decrease regional deposition of the drugs.[33]

The Blood–Brain Barrier

The BBB is primarily constituted by tight junctions between the endothelial cells that severely restrict migration of molecules from the blood into the brain tissue. In other capillary beds, there are clefts between the endothelial cells that permit passage of molecules. However, in the brain, the tight endothelial junctions permit only transcellular migration of molecules by diffusion, by carrier transport, or rarely by pinocytosis.[36,37] Abnormalities of endothelial tight junctions are seen with brain tumors and could be responsible for tumor-related brain edema.[38] Morphologically, endothelial cells of brain arteries, compared with other regions of the body, are rich in mitochondria. These mitochondria are also larger in size. This suggests that endothelial cells are metabolically very active.[39–41] Endothelial cells also are rich in metabolic enzymes such as catecholamine methyltransferase, monoamine oxidase, and adenosine deaminase,[42] which create a chemical barrier to drugs, such as catecholamines and adenosine.[43] In general, small nonpolar lipid soluble drugs can easily penetrate the BBB by passive diffusion. In contrast, the effective delivery of macromolecules that include antineoplastic drugs and nucleotides is possible only when the BBB is disrupted.[44]

Physiologic Compartments in the Brain

The brain is best described in terms of three compartments: blood, cerebral spinal fluid, and brain parenchyma. The brain tissue itself can be further divided into gray and white matter. Additional compartments might be created within the brain parenchyma that have their own kinetic characteristics in pathologic states (fig. 2).[10] Consequently, under physiologic conditions, there are

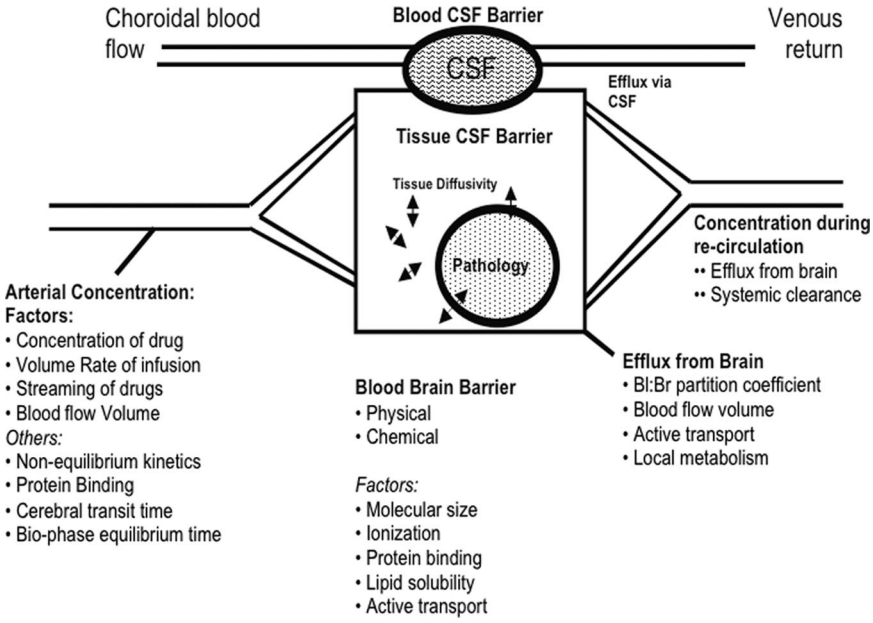

Fig. 2. Schematic representations of the compartments in the brain and the complex kinetics of intracarotid drug delivery. Brain parenchyma is not a homogenous entity and is separated into gray and white matter. *Bidirectional arrows* represent the "diffusivity of the drugs" within the brain parenchyma. Pathologic lesion (Pathology) may create additional tissue compartments. Three barriers separate the compartments: blood–brain, blood–cerebral spinal fluid (CSF), and CSF–brain. Of the three, the blood–brain barrier is the most significant. From Joshi *et al.*[71]; used with permission.

three interphases between the compartments in the brain of which the BBB is the most significant.[44] The BBB has been regarded as the gatekeeper to the brain. Compared with the blood– cerebrospinal fluid interphase, the BBB has 5,000-fold greater area and has much lower permeability.[45]

Kinetics of Intracarotid Drug Infusions

Figure 3 shows the simple kinetic framework described by Dedrick[10] demonstrating the advantage of intracarotid injection. If C_1 and C_2 are the regional and systemic drug concentrations, the pharmacokinetic advantage of intracarotid (ic) over intravenous (iv) infusion can be defined as

$$R = (C_1/C_2)_{ic}/(C_2/C_1)_{iv}.$$

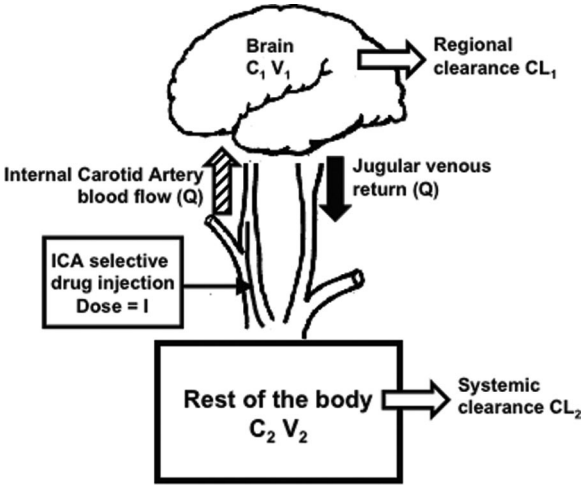

Fig. 3. Model of intracarotid drug delivery. C_1, C_2 and V_1, V_2 are the concentrations and volumes in a brain (1) and the remaining body (2), respectively. Q is the arterial blood flow and venous return. CL_1 and CL_2 are the cerebral and the remaining body clearances. ICA = internal carotid artery. From Dedrick[10]; used with permission.

In figure 3, I is the rate of drug infusion, Q is the regional blood flow, E is the first-pass extraction of the drug from the region, and CL_1 and CL_2 are the clearances from the region and from the rest of the body. CL_{TB} is clearance from the whole body ($CL_1 + CL_2$). R can also be derived as

$$R = 1 + CL_{TB}/Q(1 - E). \quad (1)$$

If $CL_1 = 0$, then

$$R = 1 + CL_{TB}/Q. \quad (1a)$$

Conversely, if $CL_2 = 0$, then

$$R = 1/(1 - E). \quad (1b)$$

Equation 1 and its derivatives 1a and 1b show that the maximum advantage of intracarotid drug infusion is evident (1) with drugs that have high CL_{TB}, (2) when the regional arterial flow (Q) is low, or (3) when the regional extraction is high. For example, we can illustrate the advantage of intracarotid delivery of propofol using equation 1a. Assuming an ICA flow to be 200 ml/min and CL_{TB} of propofol to be 2,100 ml/min for a 7-kg individual, R propofol will be 1 + 10.5 = 11.5. This theoretical number is fairly close to the observed experimental results showing a 10-fold reduction in dose of propofol required to produce electrocerebral silence with intracarotid delivery compared with intravenous infusion.[46] Conversely, the possibility of achieving high intracarotid concentrations also suggests that intracarotid infusion might result in locally toxic drug concentrations without any evidence of systemic toxicity.

Pitfalls in Kinetic Modeling of Intracarotid Drug Infusions

There are several assumptions in the kinetic model proposed by Dedrick.[10] These include uniform mixing of drug in the blood, determining free drug concentration based on conventional steady state drug–protein interactions, constant clearances over time, constant regional blood flow, homogenous distribution within the arterial irrigation, and homogenous behavior of the brain compartment. Two of these assumptions merit close scrutiny:

Estimation of the Free Drug Concentration after Intracarotid Injection. According to the "free-drug hypothesis," it is the free drug in the plasma that is available for diffusion across the BBB. However, *in vivo* during intracarotid injections, the tissue brain concentrations are higher than those predicted by the free-drug hypothesis. Jones *et al.*[47] compared the uptake of different benzodiazepines after intracarotid bolus injection in rats. They found that the brain uptake of this class of drugs was largely determined by their lipophilicities. However, *in vitro* modeling grossly underestimated the *in vivo* uptake of these drugs. They determined that observed *in vivo* data deviated from the more theoretical model with higher doses of albumin that were injected along with the drug. The free drug concentration seemed to be 5- to 25-fold greater *in vivo* than predicted by *in vitro* observations.[47] Several possible explanations have been offered for this observation. First is the "free-intermediate hypothesis," which states that rapid uptake of a drug into the brain enhances the release of drug bound to plasma proteins.[48,49] The second possibility is that other proteins in the blood have higher drug affinity, such that *in vitro* estimates of free drug concentrations based on albumin binding alone underestimate the blood concentrations.[49,50] The third possibility is that there might be some drug–protein binding competitor in the capillaries that increases the drug–protein dissociation rate.[51] Fourth, when drugs bind to proteins, they are absorbed by a peptide transporter system, which may increase transfer across the BBB.[52]

Heterogenous Nature of Brain Compartments. It is best to consider the brain parenchyma in terms of separate compartments with distinct units as described previously: (1) gray matter, (2) white matter, and (3) pathologic compartments, such as tumor or ischemic regions, within the brain parenchyma.[53,54] These compartments will differ with respect to their blood flow, BBB functions, and ability to extract and metabolize drugs. For example, the blood flow to the gray matter (50 ml · 100 g^{-1} · min^{-1}) is approximately twofold greater than in the white matter (25 ml · 100 g^{-1} · min^{-1}) and fourfold greater than in the ischemic regions (12 ml · 100 g^{-1} · min^{-1}).[55] Baseline variability in regional blood flow could result in differences in drug concentrations in the brain tissue compartments after intraarterial injection.[10] Eventually, effective modeling of intracarotid drug delivery will require an understanding of the micropharmacokinetic factors that determine drug distribution within the brain tissue (fig. 4).[56]

Theoretical Advantages of Intracarotid Drug Delivery

Intracarotid infusion of drugs offers the following theoretical advantages:

High Regional Arterial Concentration

Intracarotid drug infusion can restrict the initial volume of distribution to one cerebral hemisphere. The volume of blood flow through the ICA in humans has been estimated to be approximately 200 ml/min, whereas the cardiac output is 5–6 l/min. Conse-

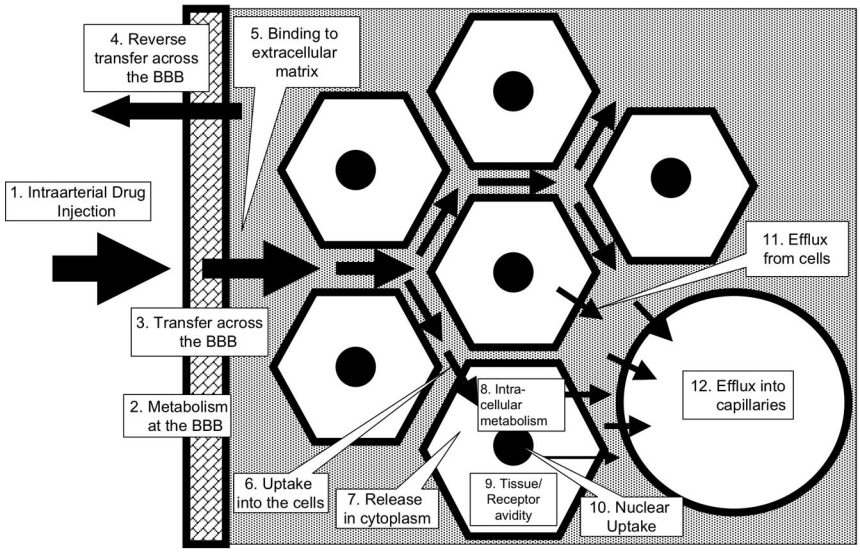

Fig. 4. Micropharmacokinetics of drug delivery to the brain: potential factors that could affect drug concentrations at it specific site of action. BBB = blood–brain barrier. From Wang and Joshi[56]; used with permission.

quently, drugs that are infused into the small volume of ICA flow achieve relatively high initial arterial concentrations at low total doses, thereby decreasing systemic toxicity.[46,57,58]

High Free Drug Concentrations

Although the exact nature of the interactions between the drug and binding proteins after intracarotid infusions remains to be fully understood, limited data suggest that intracarotid administration of drugs results in disproportionately higher free drug concentrations than those predicted by steady state kinetic models.[47] Recent videomicroscopic images have revealed that bolus injections of drugs transiently overwhelm the blood flow and may deliver virtually undiluted drug to the brain.[59] Such injections, in theory, would considerably attenuate the decrease in free drug concentration due to protein binding or the uptake by blood cells. Manipulating the key parameters of bolus injection, volume, concentration, and frequency can have a significant effect on the tissue concentrations of intracarotid drugs.[59] Bolus injections, when combined with regional blood flow manipulation, could therefore significantly enhance intracarotid drug delivery.[34]

Rapid Onset of Action

Intracarotid delivery can achieve rapid, virtually instantaneous, high drug concentrations in the brain. Such an ability to instantaneously generate high tissue concentrations may be critical in some clinical situations, such as preventing reperfusion injury after intracarotid thrombolysis.[60–62]

Theoretical Disadvantages of Intracarotid Drug Delivery

The theoretical disadvantages of intracarotid infusions can be summarized as follows:

The High Resting CBF as a Disadvantage

As the target organ, the brain, with a relatively high resting blood flow that amounts to 15–20% of the cardiac output, is at a disadvantage compared with some other less-well-perfused organs.[63] High blood flow decreases the peak drug concentrations due to greater dilution by the arterial blood. Increased blood flow to the brain could decrease the drug transit time through cerebral circulation if the cerebral blood volume was not proportionately increased. Transit time seems to have a direct effect on tissue concentrations of highly lipid-soluble anesthetic drugs after intracarotid injections.[56] In addition, high blood flow will augment drug efflux from the brain tissue.

Kinetics of Intracarotid Drugs Are Difficult to Model

For example, under physiologic conditions, the brain has at least three compartments: gray matter, white matter, and cerebrospinal fluid. These compartments demonstrate unique kinetic characteristics. Pathologic tissue, such as cerebral edema or brain tumor, may have significantly different kinetic properties. These factors may make it difficult to model drug kinetics in physiologic and pathologic states and has led to the failure of theoretical models of intracarotid drug delivery.[64]

Loss of Intracarotid Dose Advantage over Time

The advantages of intracarotid *versus* intravenous drug delivery decrease with prolonged infusions due to lower peak regional concentrations and the eventual redistribution of the drug. Computer simulations suggest that intracarotid drug infusion over 2 h *versus* the same dose infusion over 10 h results in regional concentrations that are 5.5- and 3.1-fold greater than intravenous delivery, respectively.[10] Experimental data also suggest that the comparative dose advantages of intracarotid *versus* intravenous drug delivery decrease when infusions are used for prolonged periods of time. In rabbits, intracarotid propofol achieves transient electrocerebral silence at one tenth the intravenous dose. On the other hand, to maintain electrocerebral silence for 1 h, intracarotid delivery is only 5-fold as effective as the intravenous injection.[46]

Brain Tissue Drug Concentration Measurements Are Challenging

Measurements of drug concentrations are particularly challenging with intracarotid drug delivery to the brain. Postmortem samples do not provide time histories.[65] Multiple tissue biopsies, though feasible, tend to injure the preparation and are not site specific.[66] Insights into the field have been limited to a few magnetic resonance imaging positron emission tomography studies and a few radiolabeled drug–based studies.[47,67–70] The α half-life of many lipid-soluble drugs, such as carmustine and propofol, is exceedingly short, ranging between 1.4 and 7 min.[68,71] Microdialysis requires time to obtain sufficient sample for analysis, is invasive, and may alter tissue characteristics.[72,73] Therefore, the exceedingly rapid changes in tissue drug concentrations, particularly after bolus injections, are beyond the time resolution of microdialysis. Novel optical techniques, such as diffuse reflectance spectroscopy, can noninvasively measure tissue drug concentrations in virtual real time, which could provide better understanding of intracarotid drug kinetics.[74,75]

Practical Methods to Improve Intracarotid Drug Delivery

From the practical standpoint, intracarotid drug delivery could be improved by the following means:

Disrupting the Blood–Brain Barrier

Controlled disruption of the BBB can be achieved by either hyperosmotic agents or chemical means.[76,77]

Hyperosmotic Disruption

Intracarotid injection of hypertonic substances such as mannitol and arabinose leads to a transient loss of BBB functions (fig. 5).[78] Hypertonic agents cause vasodilation and shrinkage of the endothelial cells, resulting in increased diffusivity and bulk flow across the BBB.[77] Cell shrinkage, along with the contraction of the endothelial cytoskeleton, results in widening of the tight junction to approximately 20 nm, which results in a 10-fold increase in permeability of some compounds. Alternately, some believe that mechanisms other than cell shrinkage, such as alterations in Na^+–Ca^{2+} exchange, might play a role during osmotic disruption of the BBB.[79] The effects of hypertonic mannitol were previously thought to be exceedingly transient, although data suggest that in humans, hypertonic BBB disruption lasts for 30 min and BBB functions remain impaired for several hours afterward.[80] Zunkeler *et al.* showed that the healthy BBB was almost 15-fold more susceptible to osmotic disruption than the BBB in glioma tumors.[81,82] Biomechanical factors such as systemic hypotension seem to mitigate osmotic disruption of the BBB, whereas hypertension enhances disruption.[83,84] In experimental settings, the efficacy of hypertonic mannitol can also be enhanced either by cooling the solution to 4°C or with a Na^+–Ca^{2+} exchange blocking drug, KB-R7943.[85,86] There is evidence to suggest that treatment with steroids, anesthetics, and magnesium can mitigate BBB disruption by intracarotid mannitol.[87–90] Restoring BBB functions after intracarotid mannitol may help in limiting the complications of hypertonic mannitol therapy.[88,91–93]

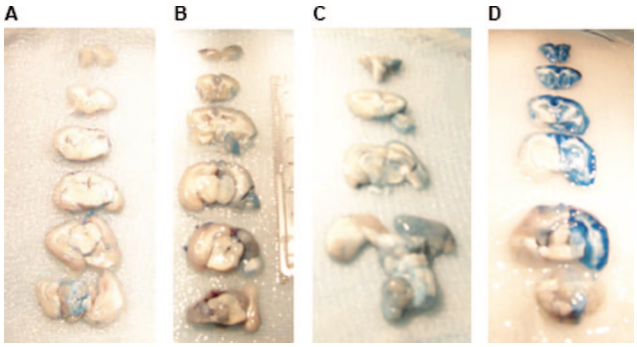

Fig. 5. Disruption of the blood–brain barrier with intracarotid mannitol. The figure shows the disruption of the blood–brain barrier by intracarotid injection of mannitol (25%) in New Zealand White rabbits as evidenced by the distribution of 2% Evans blue dye: 2-ml (*A*), 4-ml (*B*), 6-ml (*C*), and 8-ml (*D*) mannitol bolus injected through the carotid artery in 1 min. From Wang *et al.*[83]; used with permission.

Chemical Disruption of the Blood–Brain Barrier

Chemical disruption of BBB by intracarotid injection of bradykinins such as Cereport (RMP-7) or leukotrienes (LTC-4) results in transient opening of the BBB.[76] Contrary to the disruption by mannitol, disruption of the BBB by Cereport and leukotrienes seems to be limited to pathologic lesions and not normal brain. The effects of the drug are reversible within 30–60 min. Cereport can increase the uptake of intraarterially delivered antineoplastic drugs.[94,95]

Superselective Intracarotid Delivery of Drugs

One of the ways to minimize the side effects of intracarotid drugs is to restrict their delivery to pathologic lesions by superselective cannulation of the feeding arteries. With the development of highly flexible flow directed catheters with external diameters of 1.5–2 mm, it is possible to cannulate distal branches of the carotid artery without the risk of obstructing the blood flow (fig. 6).[96] The problem with distal cannulation is the increased risk of streaming (see Streaming of Drugs section).[97] However, side port catheters and diastolic pulse delivery can minimize the chances of streaming.[98] The theoretical advantages of superselective delivery of drugs include minimizing the total dose, decreasing the risk of regional toxicity, and limiting potential vascular complications to the pathologic regions of the brain. In case of intracarotid vasodilators, superselective infusions will decrease the chances of cerebral steal or the likelihood of an increase in intracranial pressure (ICP). A key concept recently introduced by Gobin *et al.*[14] was to determine the dose of intracarotid drugs based on a spatial fractionation algorithm. The algorithm calculates the intracarotid dose requirements during superselective drug injections based on the volume of tissue perfused by a given intracranial artery. Such an approach decreases the risks of neurologic complications during intracarotid chemotherapy.

Localizing the Drug Effects

Intracarotid infusions can be further targeted to the brain by enhancing their removal from the systemic circulation, by extracorporeal removal, by forced alkaline diuresis, or by neutralizing the effects of a drug by the coadministration of a systemic antidote.[3,99] The use of drugs, such as adenosine, with exceedingly short biologic half-lives greatly minimizes the risks of systemic side effects and could potentially lead to "fire-and-forget" types of intraarterial drug interventions.[58]

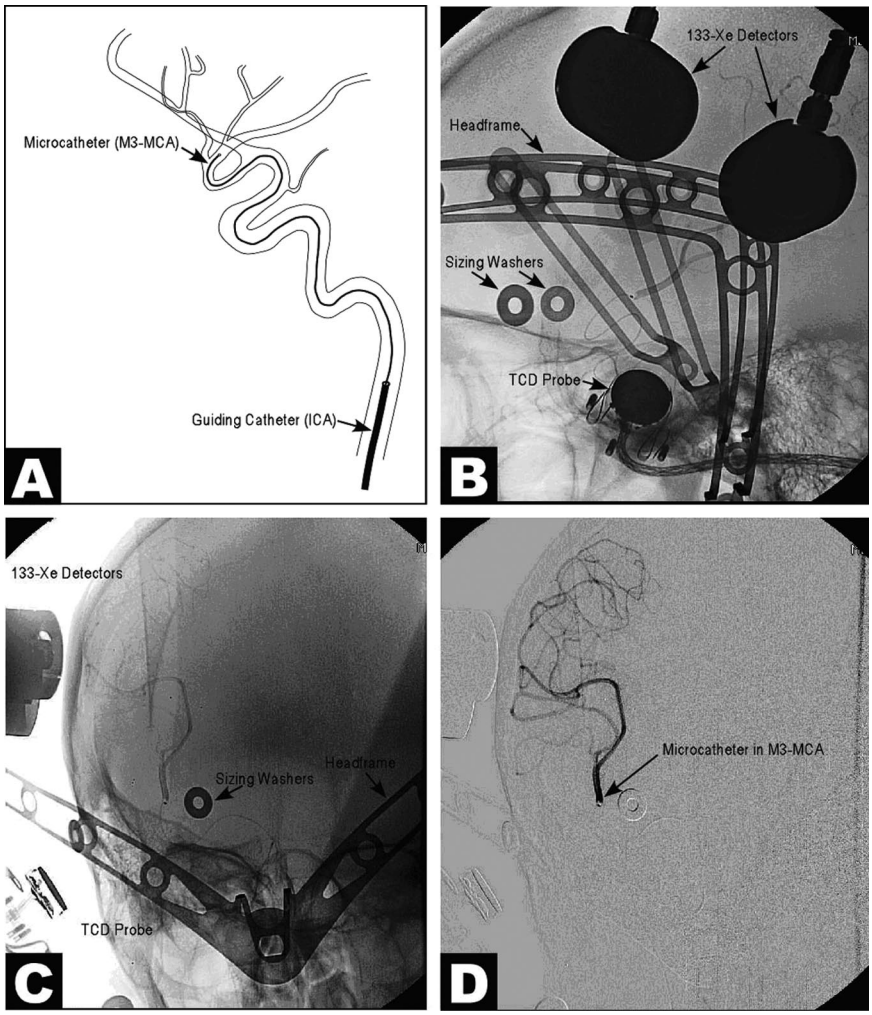

Fig. 6. Superselective placement of microcatheters in the distal regions of the brain. Microcatheters of 1.2- to 1.8-French sizes can be navigated into the distal brain for delivering drugs; measuring physiologic parameters, such as pressure and blood flow; and repairing blood vessels. Typically, two to three coaxial catheters are used. The first catheter, not shown in the figure, is located in the femoral artery (the introducer sheath). The second catheter is placed in the internal carotid artery (ICA) guiding catheter, and the third catheter (microcatheter) is guided in the distal regions of the brain (*A*). In this example, catheters are being used for measuring change in arterial blood pressure, cerebral blood flow, and cerebral blood flow velocity to determine the site of effect of intracarotid vasodilators. *B* and *C* show the placement of detectors. The model can be used to determine changes in proximal arterial resistance and can estimate changes in the cerebral arteries that lie distally beyond the tip of the microcatheter (*D*). MCA = middle cerebral artery; TCD = transcranial Doppler; Xe = xenon. From Joshi *et al.*[96]

Manipulating CBF to Increase Drug Delivery

Early computer simulations showed that intracarotid drug delivery to the brain is particularly useful in low-blood-flow states.[10] In a series of experiments, CBF was altered by changing ventilation, by augmenting blood flow with intracarotid verapamil pretreatment, or by producing transient flow arrest. The dose of an intracarotid anesthetic, propofol, required to produce electroencephalographic silence, was directly related to the blood flow.[33] Both hypercapnia and verapamil pretreatment, which increased CBF, increased the dose requirements of intracarotid anesthetics, whereas flow arrest significantly increased the duration of electroencephalographic silence after bolus anesthetic injection (figs. 7 and 8).[33,34]

Practical Concerns with Intracarotid Drug Delivery

There are several significant practical concerns with regard to intracarotid drug delivery to the brain:

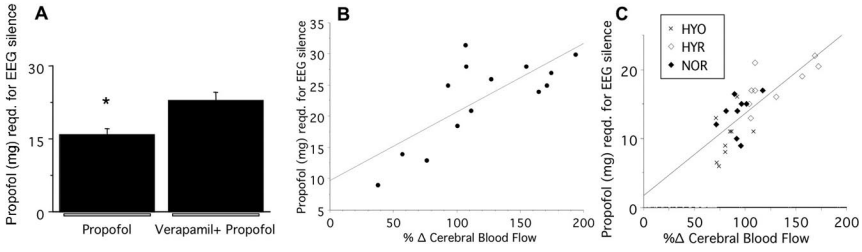

Fig. 7. Effect of blood flow on the dose requirements of intracarotid propofol. Intraarterial verapamil is a potent cerebral vasodilator. (*A*) The dose of intracarotid propofol required to produce 10 min of electrocerebral (electroencephalographic [EEG]) silence significantly increases with verapamil pretreatment (n = 14, $P = 0.004$). (*B*) The dose requirement of propofol is linearly related to the increase in blood flow after verapamil pretreatment ($r = 0.75$, $P = 0.0021$). (*C*) Increase in cerebral blood flow with changes in ventilation directly affects the dose of propofol required for electrocerebral silence. HYO = hypocapnia; HYR = hypercapnia; NOR = normocapnia. Adapted from Joshi *et al.*[33]

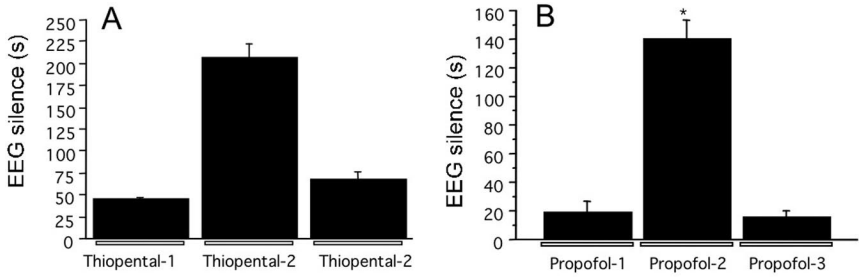

Fig. 8. Increase in the duration of electroencephalographic (EEG) silence with intracarotid anesthetic drugs injected during transient cerebral hypoperfusion (CHP). The duration of EEG silence after intracarotid injection of thiopental (3 mg as 1% solution, *A*) and propofol (3 mg as 1% solution, *B*). In thiopental-1 and -3 and propofol-1 and -3, injections were undertaken with normal blood flow; whereas the second injections (thiopental-2 and propofol-2) were made during transient CHP. During transient CHP, the blood flow decreased to 10–20% of baseline for less than 60 s. The effects of the anesthetics were significantly prolonged when they were injected during CHP. Adapted from data in Joshi *et al.*[33,34]

The Risk of Embolism and Hemorrhage during Endovascular Interventions

Recent review suggests that the incidence of neurologic complications after endovascular procedures varies a great deal, from 5.6% during the placement of a carotid stent to 19% during occlusion of a parent artery in the treatment of cerebral aneurysms.[100] A significant factor contributing to this morbidity is cerebral embolism due to thrombi, dislodged atheromatous plaques, or air emboli. A number of strategies are being developed to interrupt the thromboembolic pathway. Soft, flow-guided catheters can decrease the risk of endothelial injury. Adhesion, activation and aggregation of platelets can be inhibited with agents such as aspirin, ticlopidine, and clopidogrel. The coagulation cascade can be blocked by inhibiting the activation of fibrinogen by thrombin. The antithrombin effects (as well as the potential adverse effects) of heparin are well known, can easily be monitored by measuring the activated clotting time, and can be easily reversed with protamine. Therefore, heparin provides convenient thromboembolic prophylaxis in clinical settings. Although heparin has been the mainstay of thromboembolic prophylaxis during endovascular surgery, newer strategies, such as hirudin analog or platelet receptor antibodies, may find wider application in the future.[101] Endovascular interventions in the background of significant anticoagulation carry a greater risk of hemorrhagic stroke as a complication. Catastrophic bleeds during the procedure necessitate immediate and aggressive endovascular and surgical interventions. Rapid reversal of the anticoagulant effects of heparin with protamine is particularly useful in such situations. A well-thought-out management strategy should be in place before anticoagulation.[102]

The risk of thromboembolism is also directly related to the duration of endovascular catheterization. Prolonged catheterization of the cerebral arteries can permit repeated cerebral angiography to monitor response or facilitate delivery of drugs. Retrograde cannulation of the superficial temporal arteries was used to permit cerebral angiography over a week without any complication in patients with intracranial aneurysms.[103] Kallmes *et al.*[104] have used a swine model to demonstrate that catheters with hydrophilic surfaces were less thrombogenic than those with hydrophobic surfaces. The risk of thromboembolism also depended on the catheter material not just surface coating. In this model, long-term implantation of a microcatheter was well tolerated for the longest duration of the study, 35 days.

Air Embolism

One of the less-recognized risks of intracarotid drug therapy is the accidental injection of air, sometimes dissolved in fluids. Studies with transcranial Doppler flow measurements have revealed a frequent occurrence of microscopic air emboli during angiography. Microscopic air entrainment is likely to occur at two times during the angiographic procedure: during the aspiration of contrast into the syringe and during the injection of contrast. Increased viscosity of contrast increases the risk of air entrainment. The chances of air emboli being injected are decreased if the syringes are allowed to stand. The risk of air embolism is directly related to the rate of injection and inversely related to its viscosity. Therefore, decreasing the rate of injection decreases the chances of air embolism.[105]

Streaming of Drugs

Streaming of drugs refers to the uneven distribution of drugs in the arterial stream that results in different drug concentrations within that arterial distribution.[106] Streaming has been observed *in vivo* and *in vitro* and has been invoked to explain focal drug toxicity of chemotherapeutic agents within arterial distribution (figs. 9 and 10). Using a polystyrene cast of human cerebral arteries, it has been shown that streaming depends on the rate of drug infusion, the type of catheter used for drug delivery, and the position of the catheter in relation to the arterial branching. This *in vitro* model suggests that there can be an almost 5-fold difference in drug concentrations due to streaming.[107] In a human study using O^{15} positron emission tomography, Saris *et al.*[98]

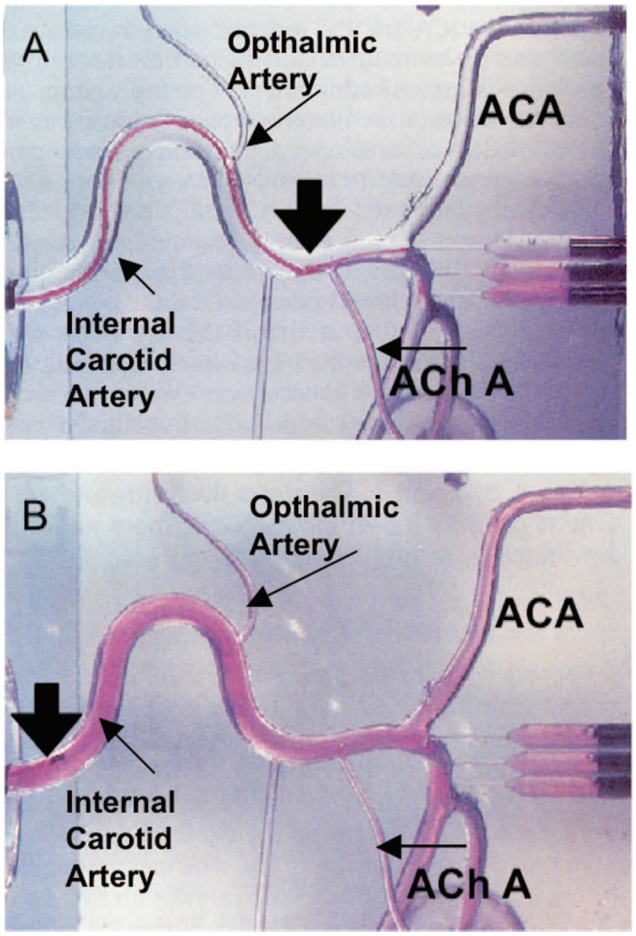

Fig. 9. Factors that influence the extent of streaming in an *in vitro* model of human cerebral arteries. *A* shows streaming of the dye (2 ml/min) from a P-100 catheter in a supraophthalmic position (*bold vertical arrow*). Note that there is a clear stream of dye in the anterior choroidal artery (Ach A) and that there is no flow of the dye to the anterior cerebral artery (ACA). *B* shows a more homogeneous dispersion of the dye when it is injected in an infraophthalmic location at a rate of 17 ml/min. A proximal site and a high rate volume rate of infusion, decrease the variability in drug concentration due to streaming. From Lutz *et al.*[107]; used with permission.

demonstrated that there can be an 11-fold variation in regional drug concentration within the arterial irrigation of the supraophthalmic segment of the ICA.

Local versus *Systemic Toxicity*

The delivery of drugs directly into the brain has been associated with regional toxicity. There is an increased incidence of white matter lesions with intracarotid chemotherapy compared with intravenous therapy.[108,109] Streaming is also thought to be responsible for retinal injury after intracarotid infusion of antineoplastic drugs.[110] Therefore, in defining toxicity, one has to factor in the total dose of the intraarterial drug, as well as the highest possible concentration that might result from inadequate mixing. In addition, possibility of injury to blood vessels, such as to the vascular endothelium, should also be considered.[111,112]

Standardizing the Dose of Intracarotid Drugs

One of the major problems in intracarotid drug therapy is the standardization of doses within individuals of the same species or during the extrapolation of data between animals of different species. Doses have been described in terms of weight/unit body surface area,[113] total milligram dose, or infusion rates in mg/min, and dose/kg body weight. Investigators have also assessed the response to intracarotid drugs as a function of estimated molar concentrations.[114–116] In the absence of any consistent way to present dose data, it is sometimes difficult to compare drug response in different studies. We recommend that to optimally interpret intracarotid dose–response data, one has to consider all three infusion parameters: (1) The rate of drug infusion (mg/min, or mol/min), which, along with the blood flow, determines peak concentrations. (2) Estimated concentration in arterial blood, *i.e.*, dose of drug/volume of blood flow in the infused artery. With superselective infusions, drug concentrations may be estimated by the volume of tissue infused based on angiographic measurements.[117] (3) The total dose when it is sufficient to cause systemic toxicity.

The exact description of intracarotid doses is particularly important in extrapolating the doses from one animal species to another. Because of the differences in relative sizes of various organs, scaling of intracarotid doses merely on the basis of body weight or body surface area can lead to errors. For example, within individuals of a given species, parameters such as blood flow in the ICA can be assumed to be relatively constant, but across animal species, those assumptions may not be valid. Therefore, the same amount of drug will generate different arterial blood concentrations. Because of the relatively large size of the brain and higher carotid arterial blood flow, primates tolerate a much higher dose of intracarotid drugs compared with rodents or dogs. To undertake intraspecies comparisons, Dedrick[118] described kinetic models based on organ size and surface areas. These relative sizes of organs differed between species but their function and surface characteristics were similar. Even when such allometric corrections are made, it is still difficult to project intracarotid kinetic data from one animal species to another.

Clinical Applications of Intracarotid Drug Delivery

Intracarotid Anesthetics for the Localization of Brain Functions

More than 50 yr ago, Wada developed the technique of injecting sodium amytal into the carotid artery.[1] The procedure was originally developed to permit unilateral electroconvulsive therapy but subsequently became a standard method for localizing language function and memory. Other anesthetic drugs that have been used for Wada testing include methohexitone and, recently,

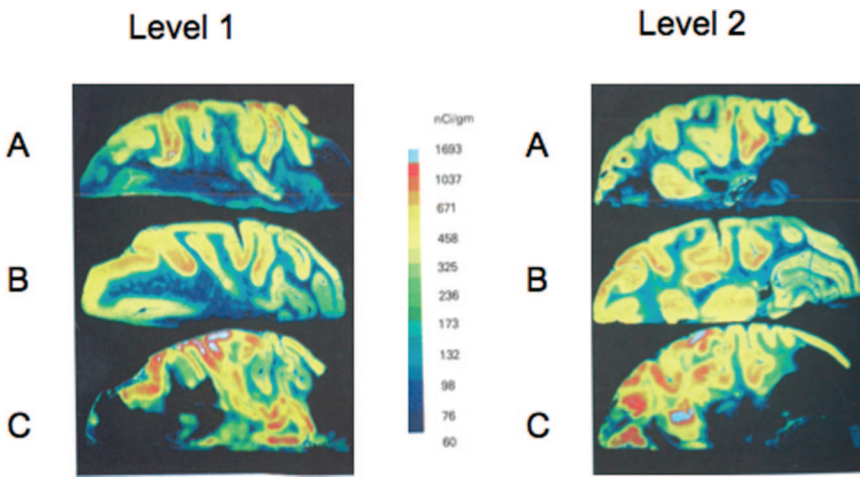

Fig. 10. Effect of the method of drug injection on the distribution of intracarotid drugs. Reconstructed autoradiographic images show distribution of tracer at two levels of a nonhuman primate brain, frontoparietal cortex (level 1) and through basal ganglia and the temporal lobe (level 2). (*A*) Injection of intracarotid tracer as pulses during diastole shows homogenous tissue drug concentrations. (*B*) Intravenous infusion of drugs also produces similar homogenous concentration. (*C*) Intracarotid infusion of the tracer produces marked variations in tissue tracer concentrations due to streaming. These results suggest that injection of intracarotid drugs as diastole-phase pulses considerably decreases variations in tissue drug concentrations due to streaming. From Saris *et al.*[157]; used with permission.

propofol.[1,119–122] Compared with amytal, intracarotid methohexitone seems to have a shorter duration of effect, thereby making it possible to test multiple arterial territories in the same setting.[122] However, there seems to be poor justification for the selection of intracarotid doses.[71] Most radiologists use a graded dose of 75–125 mg amytal mixed with contrast media. After an initial dose of 75 mg, additional boluses of 25 mg are injected until there is an upper limb drift. Speech, language, and memory functions are assessed as the deficit resolves. Intracarotid amytal in doses as high as 3 mg/kg or 200 mg has been used during the Wada test. Such high intracarotid doses of anesthetic drugs on recirculation suppress the contralateral hemisphere. Any additional baseline sedation provided by an anesthesiologist in attendance would further complicate the interpretation of the Wada test. Therefore, it has been recommended that when high doses of amytal are used, the contralateral hemisphere should be tested on a subsequent day.[123]

In recent years, there has been considerable interest in the use of propofol for Wada testing.[120] In a recent study, however, as many as 19 of 58 patients developed transient neurologic symptoms. These consisted of tonic movement, confusion, and pain. The symptoms were seen when more than 10 mg of the drug was rapidly injected in patients older than 55 yr. None of these patients had any permanent complication, but the authors recommend limiting the dose of propofol to 10 mg and careful monitoring in patients older than 55 yr.[124] Despite these recent reports with propofol, the safety of the Wada test is underscored by the fact that the test has been widely used for a very long time. Although neurologic complications have been reported due to arterial emboli, they do not seem to be frequent.[125]

Superselective Wada testing is also used before embolization of cerebral arteriovenous malformations (fig. 11). Because embolization of the lesion could injure both gray and white matter, injection of amytal is combined with injection of lidocaine to test for both the gray and the white matter. Amytal is injected first to suppress gray matter activity, followed by the injection of lidocaine to suppress nerve conduction through the white matter. Anesthesiologists involved in the care of patients undergoing Wada tests should use judicious amounts of sedation. Both propofol and dexmedetomidine have been used for the purpose. Midazolam may impair memory testing and therefore has to be used cautiously.

Cerebral Vasospasm

Cerebral vasospasm is a pathologic narrowing of the cerebral arteries. The fundamental method to overcome this added arterial resistance, whether proximal or distal, is to increase the cerebral perfusion pressure and the cardiac output by using hypervolemic hemodilution with induced hypertension (triple-H treatment).[126] A significant number of patients with cerebral vasospasm do not respond to triple-H treatment. Furthermore, triple-H treatment has to be carefully applied to patients with untreated or multiple aneurysms. The alternate strategy in such cases is to decrease cerebrovascular resistance by superselective intracarotid or intracarotid infusion of vasodilators.[58,117,127,128] Intracarotid papaverine has been the mainstay of such a treatment, although a variety of drugs such as calcium channel blockers, mannitol, and prostaglandin E have also been used intraarterially for treating vasospasm (fig. 12). Other drugs, such as adenosine, have been proposed for the treatment of vasospasm and, despite their significant vasodilator effects, have not yet been used in clinical settings, probably because of their short duration of effect and poor penetration of the BBB (fig. 13).

Table 1 shows the published outcomes of intracarotid vasodilator therapy. Clinically, approximately 30–60% patients seem to benefit from intracarotid vasodilators. Angiographic improvement, however, is seen much more frequently. Although there is a suggestion that intracarotid vasodilators may augment CBF, improve ce-

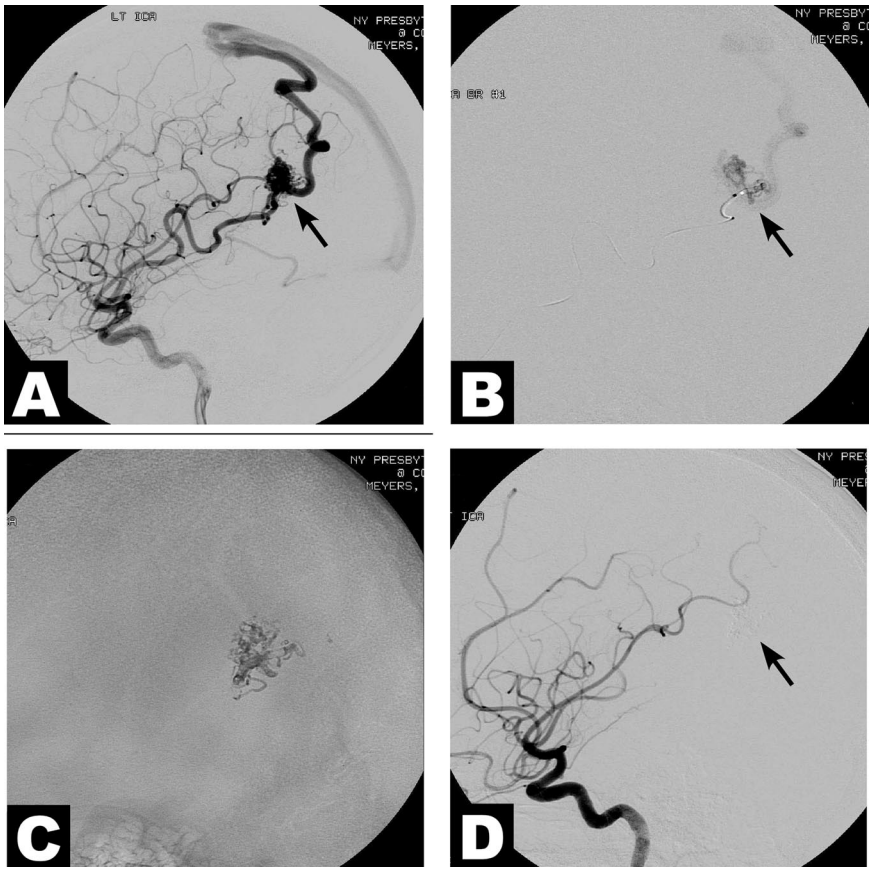

Fig. 11. Superselective Wada testing: a case report. A 32-yr-old woman with seizures and left hemicranial headaches was found to harbor a subcortical arteriovenous malformation (AVM) in the left parietal lobe. (*A*) Left carotid arteriography confirmed the presence of the AVM with multiple nidal aneurysms (*arrow*). (*B*) During local anesthesia, only a 0.5-mm diameter microcatheter was placed in close proximity of the AVM for the injection of anesthetic drugs, amytal and lidocaine, for superselective Wada testing. The testing is performed in conjunction with members of the neuropsychological service to determine the risk of causing neurologic deficits both at embolization or surgical resection. In this case, no changes in function were identified. (*C*) Fluorangiography of the cranium after the occlusion of the AVM with n-butyl-cyanoacrylate shows radio-opaque glue filling the sinusoids within the AVM nidus (*arrow*). (*D*) Control angiography after occlusion of the AVM shows complete obliteration of the AVM nidus and no other branch vessel occlusion (*arrow*). The patient tolerated embolization and resection without any complication and returned to work in 9 days. Images and case history are provided by Phillip M. Meyers, M.D.

rebral oxygenation, and reverse metabolic acidosis, the effect of vasodilator therapy seems to be transient and resolves completely over the next 24 h. By measuring the time it takes for radiocontrast to transit through the cerebral arteries and the capillary bed, one can estimate the differential effects of intracarotid vasodilators on the proximal and distal cerebral circulation. In the case of papaverine, the resistance of both the

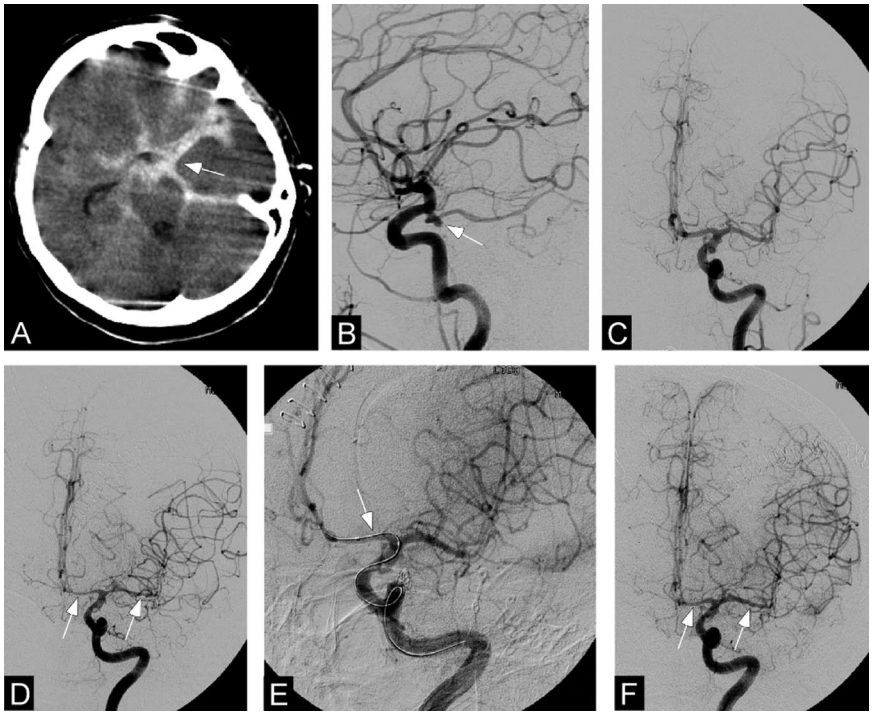

Fig. 12. Treatment of cerebral vasospasm with intracarotid verapamil. A 57-yr-old woman developed sudden severe headache and collapsed to the floor. On admission to the hospital emergency department, she was comatose with decorticate posturing. (*A*) Computed tomographic brain scan without contrast demonstrates diffuse subarachnoid hemorrhage (*arrow*). (*B* and *C*) Cerebral arteriography demonstrates a 7-mm left posterior communicating artery aneurysm (*arrow*). There is no spasm in the cerebral arteries at the time of initial presentation. (*D*) Surveillance arteriography on day 7 after the hemorrhage shows moderate to severe, flow-limiting spasm of the cerebral arteries (*arrows*). (*E*) To prevent stroke, endovascular treatment including balloon angioplasty (*arrow*) followed by vasodilator infusion therapy with 5 mg verapamil was performed. (*F*) Cerebral arteriography after treatment shows both improved vessel dimension and flow in the cerebral vasculature. Images and case history are provided by Phillip M. Meyers, M.D.

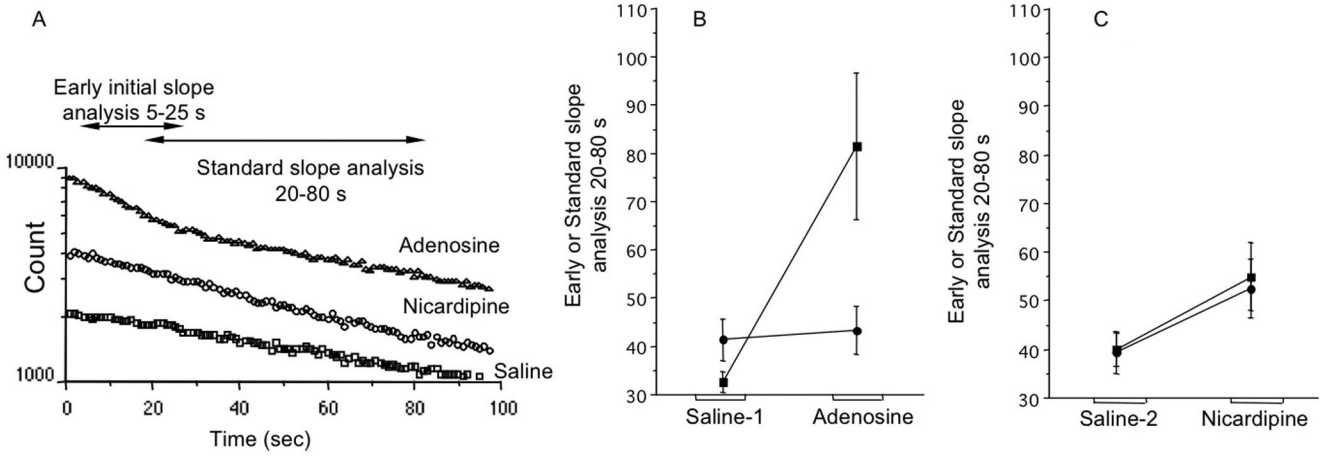

Fig. 13. Effects of adenosine on human cerebral blood flow (CBF). Adenosine is rapidly metabolized by the vascular endothelium and the erythrocytes with an elimination half-life of 1–10 s. An intracarotid bolus of 1–2 mg adenosine results in significant change in shape of the ^{133}xenon washout curve. Compare the washouts during injection of adenosine, nicardipine, and saline (*A*). The effects of adenosine bolus seem to last for less than 30 s. The conventional CBF measurements (standard initial slope analysis [standard ISI]) that are measured between 20 and 80 s after ^{133}xenon injection does not show an increase in CBF (*solid circles*, *B* and *C*) with intracarotid adenosine. However, early initial slope analysis (early ISI) that is measured between 5 and 25 s after ^{133}xenon (*solid squares*, *B* and *C*) seem to have a dramatic effect on CBF. In case of nicardipine, a longer-acting drug, the early ISI and standard ISI yield similar results. Effects of intracarotid adenosine on CBF are exceedingly transient, whereas nicardipine has a sustained effect. From Joshi *et al.*[58]; used with permission.

proximal and the distal cerebral arteries decreases during drug infusion.[35,128]

Intracarotid vasodilator therapy carries with it two general risks: cerebral steal and increase in ICP. However, neurologic complications can also result from specific drugs, *e.g.*, neurotoxicity with papaverine.[129]

Cerebral Steal. Cerebral steal has been invoked to explain the decrease in regional blood flow in proximity to focal cerebral pathology after the administration of intravenous or intracarotid papaverine.[130,131] Any decrease in hemispheric cerebrovascular resistance, whether pathologic or iatrogenic, can cause a redistribution of blood flow away from those ischemic areas where there is already maximal vasodilation. In recent years, the clinical significance of steal has been challenged as with regard to large arteries.[132] There are, however, examples of microcirculatory steal during hypercapnia or during administration of volatile anesthetic agents, such as halothane, in the setting of focal cerebral ischemia.[133,134] Unless vasodilator therapy is restricted to the arteries afflicted by cerebral vasospasm, intracarotid vasodilator therapy carries the theoretical risk of cerebral steal, due to vasodilation in the normal vascular beds.

Increase in Intracranial Pressure. Increase in ICP has been reported with intracarotid infusion of papaverine. Controversy surrounds the effect of intracarotid vasodilators on ICP. Experiments in dogs and monkeys that do not have cerebral vasospasm suggest that intracarotid vasodilators such as sodium nitroprusside increase ICP but may not increase CBF, implying that nitroprusside affects cerebral capacitance arterioles to increase cerebral blood volume with no effect on the resistance arterioles.[135] On the other hand, intracarotid infusion of adenosine has a relatively benign effect on ICP but augments CBF, suggesting that adenosine primarily affects the resistance arterioles.[136] It remains to be seen whether intracarotid therapy could selectively target proximal or distal cerebral arteries to minimize the risk of increased ICP.

Cross *et al.*[137] measured changes in ICP during intracarotid infusion of papaverine in 28 patients. The increase in ICP ranged from 0 to 60 mmHg. A baseline ICP of 15 mm or greater was associated with a greater risk of increasing ICP. However, Hunt and Hess scores, Fisher grades, age, and Glasgow Coma Scale scores on admission and immediately before treatment did not correlate with ICP increases. ICP increases result in a decrease in cerebral perfusion pressure. Therefore, hypertensive-hypervolemic interventions need to be continued during intracarotid vasodilator infusions. ICP should be monitored during intracarotid vasodilator therapy whenever feasible.

Intracarotid Papaverine. Papaverine is perhaps the most potent cerebral vasodilator. Papaverine acts through several intracellular pathways, which include cyclic guanosine monophosphate, cyclic adenosine monophosphate, phosphodiesterase inhibition, Ca^{2+} channel blockade, and histamine release. Table 1 summarizes the efficacy of papaverine and other vasodilators in the settings of cerebral vasospasm. Intracarotid papaverine can relieve angiographic narrowing, augment CBF, and mitigate neurologic symptoms in patients with cerebral vasospasm resistant to medical treatment. Typically, during the treatment of cerebral vasospasm, a dose of 300 mg papaverine is infused over 1 h.[138] Unfortunately, intracarotid papaverine infusion also results in significant neurologic complications,[139] at-

Table 1. Selected Reports of Intracarotid Vasodilators for the Treatment of Human Cerebral Vasospasm

Reference	Subjects (n)	Intervention/Drug	Significant Complications	Outcome
Suzuki *et al.*[182] (2006)	(2)	Colforsin		Improved
Oskouian *et al.*[128] (2002)	(45)	IAP ± stenting		Combined therapy more useful
Feng *et al.*[147] (2002)	SAH vasospasm (29)	IA verapamil (3 mg)	No hemodynamic complications	5/29 improved
Fortin *et al.*[183] (2000)	Catheter-induced spasm (1)	10 ml mannitol, 25%	None	Improved
Bejjani *et al.*[184] (1999)	Incidence after skull base surgery is 1.9%	Angioplasty + papaverine 5/8, papaverine 1/8, HHH 8/8		6/8 improved
Cross *et al.*[137] (1998)	SAH vasospasm (28)	IAP 300 mg/vessel	Baseline ICP ≥ 15 mm, greater risk intracranial hypertension with IAP	Increased ICP with IAP reported, ICP monitoring essential
Fandino *et al.*[185] (1998)	SAH vasospasm (10)	IAP + HHH	Combined therapy more effective	Improved jugular bulb oxygenation and reversal of lactic acidosis
Milburn *et al.*[35] (1997)	SAH vasospasm (27)			IAP decreased transit time in 58/59 territories
Touho *et al.*[186] (1997)	SAH vasospasm	IAP and HMPAO		Superselective catheterization not necessary for ACA delivery
Yoshida *et al.*[187] (1997)	SAH vasospasm (2)	Intracarotid amrinone		Angiographic response
Mathis *et al.*[141] (1994)	SAH vasospasm (3)	IAP 300 mg	Worsening in all 3, coma respiratory arrest	1 improved
Clouston *et al.*[188] (1995)	SAH vasospasm (14)	60 vascular territories: IAP 150–600 mg	1 transient blindness, 1 seizure, 1 vascular complication	7/14 markedly improved
Miller *et al.*[189] (1995)	SAH vasospasm (1)	IAP 300 mg	Thrombocytopenia	Improved
Morgan *et al.*[190] (1995)	Post-AVM resection (2)	IAP 150–250 mg	1 had neurologic deterioration	2/2 improved
Nakagawa *et al.*[191] (1994)	Vasospasm during IA chemotherapy (20)	IAP with nicardipine in 12/20 cases		Lower concentration of chemotherapeutic agents decreased complications
Kaku *et al.*[192] (1992)	SAH vasospasm (10)	IAP 200 mg with nicardipine		8/10 patients improved
Kassell *et al.*[138] (1992)	SAH vasospasm (10)	IAP 100–300 mg	2 had transient neurologic deficits	8/12 angiographic response; 4/12 improved
Boker *et al.*[193] (1985)	SAH + vasospasm (3)	Nimodipine (0.3 mg)	None	Angiographic response

ACA = anterior cerebral artery; AVM = arteriovenous malformation; HHH = hypervolemic hemodilution and hypertension; HMPAO = hexylmethylpropylene amineoxine; IA = intraarterial; IAP = intracarotid papaverine; ICP = intracranial pressure; SAH = subarachnoid hemorrhage.

tributable to several factors: cerebral steal, increased ICP,[137,140] microembolization of papaverine crystals,[141,142] neurotoxicity of the preservative (chlorobutanol),[142] proconvulsive properties of the drug,[143] and paradoxical vasoconstriction.[141]

Cerebral steal, *i.e.*, redistribution of blood flow away from the ischemic region, has often been implicated in the etiology of neurologic symptoms after intravenous or intracarotid administration of papaverine.[130,144] There is evidence that intravenous papaverine increases blood flow in ischemic regions of patients with cerebrovascular insufficiency.[145] However, experiments in cats with middle cerebral artery occlusion suggest that steal does not always occur with cerebral vasodilation. Intravenous papaverine in the feline middle cerebral artery occlusion model did not decrease regional CBF to ischemic areas as long as the blood pressure is maintained.[146]

Intracarotid Calcium Channel Blockers. Intracarotid calcium channel blockers have been used to treat cerebral vasospasm for more than a decade; however, their intracarotid administration is still not considered to be the mainstay for the treatment of cerebral vasospasm. Intracarotid verapamil, nicardipine, and nimodipine have been used for the treatment of vasospasm (table 1). There are no human studies as yet that compare the relative potencies of calcium channel blockers against papaverine. However, studies in similar groups of patients who do not have cerebral vasospasm suggest

that intracarotid verapamil, compared with papaverine, seems to be less efficacious in augmenting CBF. Verapamil in small doses (3 mg) results in angiographic improvement without systemic hypotension, although only 5 of 29 patients in this retrospective study improved clinically.[147] The modest efficacy of the calcium channel blocker might still be advantageous because it is likely to decrease the risk of cerebral steal or increasing ICP. Experimental vasospasm triggered by topical application of endothelin 1 seems to be more responsive to intracarotid nicardipine than verapamil.[148] Intracarotid nicardipine is effective in reversing cerebral vasospasm, but no study has as yet compared the potency of the various intracarotid calcium channel blockers.[149]

Intracarotid Prostaglandins. Recently, intracarotid infusions of liposomes with papaverine and prostaglandin E2 have been used for the treatment of cerebral vasospasm. Two thirds of the patients demonstrated an increase in CBF after such a treatment.[150]

To enhance the clinical efficacy of intracarotid vasodilators and decrease the risks of complications, a number of adjuvant strategies have been suggested. First, transluminal angioplasty has been used to treat cerebral vasospasm when it affects the ICA or the proximal segment of the middle cerebral artery. Angioplasty, compared with intracarotid drugs, results in a more profound and persistent increase in blood flow but it can only be used in the proximal arteries. Drugs such as papaverine are therefore useful in treating distal spasm and could be of benefit even after angioplasty.[128] Hypothermia has also been used to provide brain protection and increase the time window for intracarotid vasodilator therapy.[151] Techniques of selective brain cooling either by the infusion of cold saline or by endovascular cooling devices are currently being developed to minimize injury after vasospasm and ischemic stroke.[152–154] Finally, cocktails of vasodilators have been used so as to increase both the potency and duration of effects of intracarotid vasodilators. Therefore, papaverine has been used in conjunction with nimodipine, nicardipine, prostaglandins to enhance its safety and efficacy.[150]

The key in the anesthetic management of patients for intracarotid vasodilator treatment is to recognize the potential for exacerbating neurologic injury. These patients may present either with untreated ruptured aneurysms or after clipping of the lesion. At many institutions, triple-H therapy is instituted before intracarotid vasodilator therapy. Patients with subarachnoid hemorrhage may require inotropic support because of impaired myocardial functions secondary to hemorrhage. Ideally, management of these cases requires monitoring of the ICP so as to treat any increase by mechanical drainage, hyperventilation, or supplemental intravenous anesthesia. Furthermore, because of recirculation of intracarotid vasodilators, there may be significant systemic hypotension. Therefore, anesthesiologists should be prepared to induce hypertension to ensure adequate perfusion pressure.

Cancer Chemotherapy

The major driving force for the development of intracarotid therapies in the 1980s was the treatment of brain neoplasms. However, it soon became evident that the BBB prevented effective transfer of chemotherapeutic agents.[2] Therefore, attempts to disrupt the BBB began fairly early on.[77,94] Currently, intracarotid chemotherapy is used for the treatment of primary central nervous system lymphoma, primitive neuroectodermal tumor, germ cell tumor, cancer metastasis to the brain, and low- or high-grade glioma (fig. 14).[111] The initial response to intracarotid chemotherapy is impressive, with as many as 70–81% tumors regressing, occasionally with a significant prolongation of survival.[155,156] However, most studies have been anecdotal or uncontrolled case series. The major concern of intracarotid therapy is unexplained local toxicity, likely attributed to unusually high concentrations of the drug due to streaming. One strategy that has minimized streaming is using pulsed intracarotid infusion, which delivers the drug in the diastolic phase of cardiac cycle to increase mixing.[106,157]

The role of regional blood flow in enhancing intracarotid delivery of chemotherapeutic drugs is ill understood at this time. Some groups have suggested an increase in drug doses in proportion to the regional blood flow to safely achieve higher total doses and better tumor regressions.[14,156] At the same time, it has recently been shown that transient decrease in CBF could significantly increase delivery of anticancer drugs to the brain in a rabbit model.[15] Therefore, the exact role for the manipulation of CBF in enhancing cancer drug delivery remains to be fully understood at this time. The fundamental problem confronting investigators is the inability to rapidly measure tissue concentrations of chemotherapeutic drugs. Insights into intracarotid delivery of some anticancer drugs could be generated by optically tracking their concentrations in the brain tissue by novel spectroscopic techniques.[65,74,75]

The disruption of the BBB with intracarotid mannitol that is often needed to improve regional delivery of anticancer drugs also carries significant clinical risks.[158] Because of pain associated with the procedure, the disruption is undertaken during general anesthesia. In a recent report involving 17 patients and 210 treatment cycles, focal seizures occurred in 9 patients and in 10% of the treatment cycles. In some cases, these seizures were generalized (2 patients and 3% of treatment cycles). Chances of seizure were higher with intracarotid than with vertebral artery injections. Impaired consciousness was seen in 7.6% of patients with recovery in 24 h. One patient in this series had an intractable increase in ICP necessitating decompres-

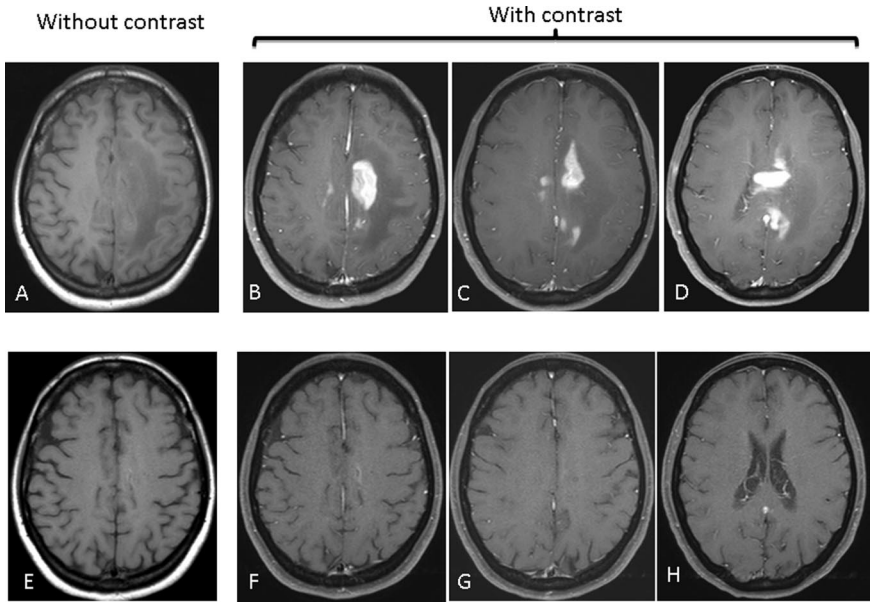

Fig. 14. Response of a lymphoid tumor to intracarotid chemotherapy. A 62-yr-old right-handed woman presented with three symptomatic white chorioretinal lesions in the right eye. A vitreal biopsy showed small lymphoid cells. Six months later, the patient started experiencing problems while walking. Magnetic resonance imaging revealed contrast-enhancing lesion in the brain (*A–D*). A stereotactic brain biopsy showed large B-cell lymphoma, CD20 positive. Cerebrospinal fluid contained 20 atypical cells/ml. The patient underwent first treatment with blood–brain barrier disruption with intracarotid mannitol and intraarterial methotrexate, and carboplatin that was supplemented with intravenous rituximab. She was admitted every 4 weeks for 2 consecutive days of the same treatment with barrier opening and intraarterial chemotherapy in one of the major brain-feeding arteries, the left or the right internal carotid or the vertebral artery. She was also treated with intraocular rituximab and methotrexate. After eight courses of treatment, there was radiologic evidence of complete tumor regression (*E–H*) without any neurologic symptoms or evidence of intraocular disease. Images and case history are courtesy of Edward A. Neuwelt, M.D. (Professor of Neurology and Neurosurgery, Oregon Health and Science University, Portland, Oregon).

sive hemispherectomy a day after treatment. Attempts to augment CBF to enhance drug delivery with intravenous atropine probably contributed to ST-segment changes seen in 4.3% of the cases, requiring β-blockade. Other complications included transient neurologic deficits (6%), postoperative nausea and vomiting despite 20 mg odansetron (11.9%), and headache (4%). Management of these patients requires a well-thought-out plan to include close monitoring of the patient's neurologic and hemodynamic status and to address significant complications that arise in the postoperative periods.[159] Patients with brain tumors may

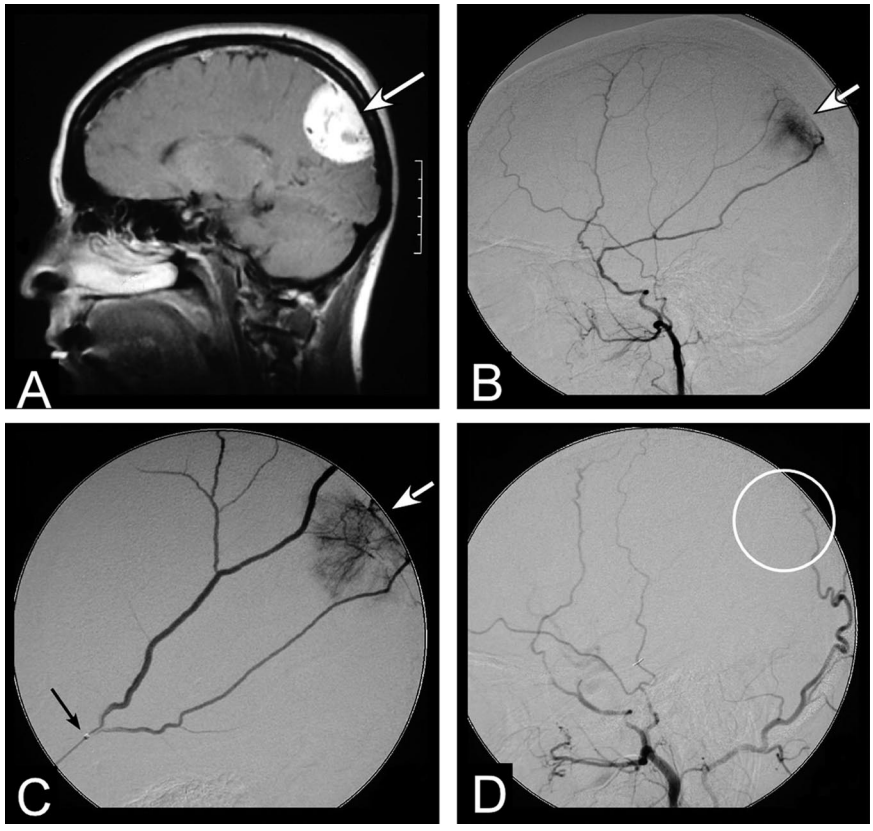

Fig. 15. Intracarotid injection of embolic materials to facilitate surgery of brain tumors. A 39-yr-old man with neurofibromatosis type II, a condition that often results in early development of multiple brain tumors, presented with hearing loss and seizures. In addition to small bilateral tumors of the vestibular nerves (not shown), the patient had developed a large extraaxial mass most compatible with a meningioma, a benign tumor that arises from the dura matter or brain covering (*A*, *white arrow*). Meningiomas are often highly vascular tumors. Before surgical removal of the tumor, the patient underwent cerebral angiography that demonstrated that blood supply to the tumor arose from branches of the middle meningeal artery (*B*, *white arrow*). With the patient awake and in a painless manner, a tiny microcatheter was advanced into the branches of the middle meningeal artery supplying the tumor (*C*, *black arrow*), and the tumor was embolized. Arteriography after embolization demonstrates that there is no longer any blood flowing to the tumor (*D*, *white circle*), indicating that the tumor could now be surgically resected with minimal blood loss. Images and case history are provided by Phillip M. Meyers, M.D.

require preoperative embolization with n-butyl-cyanoacrylate to decrease blood loss during surgery (fig. 15). These procedures are relatively painless and can usually be performed with minimal sedation.

Intracarotid Thrombolysis for Stroke

The object of intracarotid thrombolysis is to deliver high concentrations of thrombolytic drugs locally into the brain.[160] Intravenous thrombolysis can achieve a significant degree of recanalization within 3 h of onset of neurologic symptoms.[160,161] However, it is often difficult to provide thrombolytic therapy within such a narrow time window. Intracarotid delivery of thrombolytic drugs can extend the intervention time window to 6 h.[162] Intracarotid urokinase, streptokinase, and more recently recombinant tissue plasminogen activator have been used for the purpose (table 2).[163] Development of endovascular clot retrieving devices, laser or ultrasonic clot lysis techniques, and placement of endovascular stents can supplement or provide alternatives to intracarotid thrombolytic therapy.[164] Intracarotid thrombolysis is superior to intravenous thrombolysis in so far as restoring tissue perfusion, although as yet there is no clear-cut evidence of improved neurologic outcome with intracarotid thrombolysis in controlled trials (fig. 16).[165,166] Intracarotid thrombolysis today provides the most compelling reason to investigate intracarotid drug delivery to the brain. The inability to translate the results of preclinical studies with pharmacologic treatments of ischemic stroke into effective therapies compels us to develop better methods of drug delivery.[167–169] Intracarotid thrombolysis provides a unique opportunity to deliver drugs at the very site of reperfusion injury, and the catheter to do so is already *in situ*.

Because the urgency for interventions, detailed anesthetic assessment may not be feasible in stroke setting. Centers offering intracarotid thrombolysis should have an intervention suite ready to provide immediate anesthesia and should have well-established lines of communication between the stroke team and the anesthesiologists. A rapid review of medical history, last

Table 2. Selected Clinical Reports Describing Use of Intracarotid Thrombolytics for Ischemic Stroke

Reference	No. of Patients	Time/Setting	Drug and Dose	Complications	Outcome
Khatri *et al.*[60] (2005)	61 angiograms	Acute stroke	IV and IA rTPA		49–54% improved; clinical outcome was related to degree of revascularization
Abou-Chebl *et al.*[194] (2005)	12 patients	3.8 ± 2.2 h	IA rTPA, IA or IV abciximab, heparin and stent	1/12 hemorrhagic infarction	11/12 good recovery
Zaidat *et al.*[195] (2005)	96 patients	Acute stroke	IA or combined IV and IA rTPA	ICH 7.6–13.3%	24–69% recanalization was a function of time to treatment
Bourekas *et al.*[165] (2004)	36 patients	< 3 h	IA	ICH 11%	75% recanalization
Li *et al.*[196] (2003)	19 patients	Acute stroke	IA thrombolysis + stent		18/19 no stenosis
Lee *et al.*[166] (2002)	26 patients	Acute stroke	IA urokinase alone (16), IA urokinase with IV abciximab		Abciximab increased the recanalization rate and decreased the urokinase dose
Rabinstein *et al.*[197] (2002)	1 patient	< 3 h	IA rTPA		Complete recovery
Keris *et al.*[162] (2001)	12 treated, 33 controls	< 6 h	rTPA (Actilyse), 50 mg IA initially and IV subsequently	ICH	Good outcome in 66% in treatment group vs 21% in control group
Fukuda *et al.*[198] (2001)	5 patients	< 6 h	IA thrombolysis in 3/5		Recanalization achieved in all 3
Kase *et al.*[199] (2001)	120 of the 180 patients	< 6 h	IA prourokinase	ICH in 10.9% with 83% mortality	
Sylaja *et al.*[200] (2001)	5 patients		IA urokinase		2 patients treated within 3 h had complete recovery
Suwanwela *et al.*[201] (2001)	2 patients	< 6 h	IA rTPA		2/2 angiographic but not clinical recovery
Endo *et al.*[202] (1998)	33 patients	< 6 h	IA thrombolysis		Good prognosis with treatment < 3 h followed by stent or angioplasty
Jahan *et al.*[203] (1999)	26 patients	< 6 h	IA TPA	Hemorrhage in 10/26	11/26 partial or complete recanalization, 9 had good outcome; 15/26 little or no recanalization
Barr *et al.*[204] (1994)	12 patients	< 8 h	Urokinase, 160–500 K units	3/12 failed	9/12 recanalized
Casto *et al.*[205] (1992)	5 patients	< 5 h	Urokinase, 560K units		4/5 recanalized

IA = intracarotid; ICH = intracranial hemorrhage; IV = intravenous; rTPA = recombinant tissue plasminogen activator; TPA = tissue plasminogen activator.

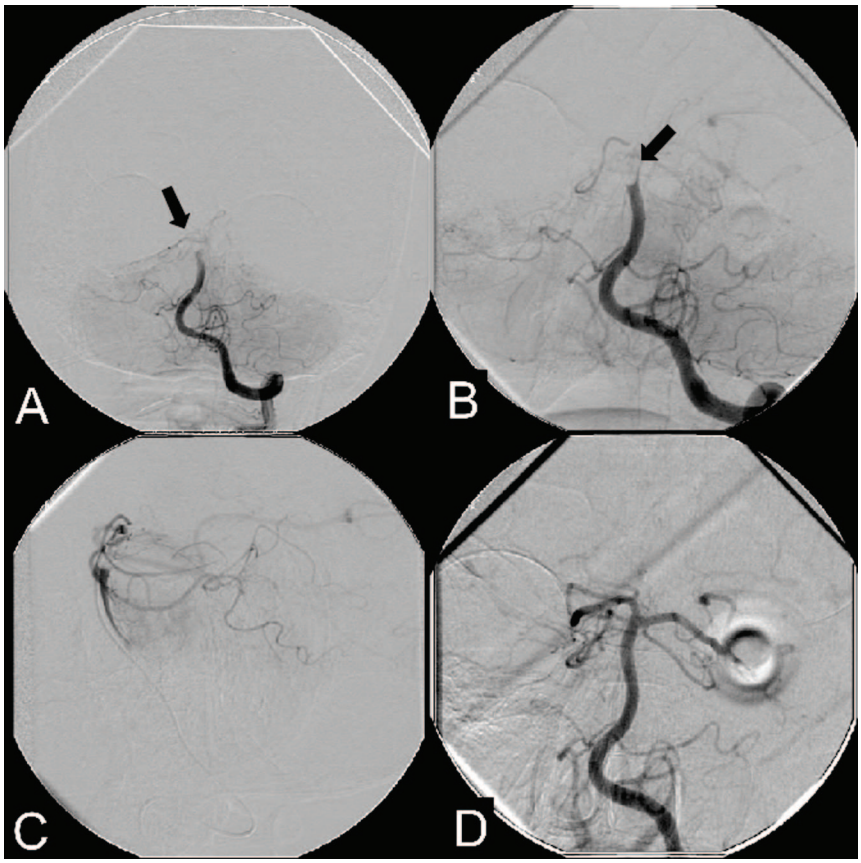

Fig. 16. Intracarotid thrombolysis in acute stroke. A 62-yr-old woman with multiple cardiovascular risk factors presented with quadriplegia followed by loss of consciousness. (*A*) Left vertebral arteriography demonstrates distal occlusion of the basilar artery (*arrow*). (*B*) On high-magnification angiography, the filling defect resulting from the occlusive thromboembolism is evident (*arrow*). (*C*) Microcatheter arteriography in the lateral projection further delineates the site of occlusion before thrombolysis with the plasminogen activator, urokinase. (*D*) After lysis of the occlusive thrombus, complete restoration of flow in the vertebrobasilar system has been restored. Images and case history are provided by Phillip M. Meyers, M.D.

meal time, drug treatments, and allergies, particularly immediate anticoagulant treatment, has to be undertaken. Airway interventions could be challenging with background anticoagulation because of the potential for hemorrhage from even minor trauma, such as placement of a nasal airway. Wherever feasible, these interventions should be performed with minimal sedation to permit neurologic examination. However, the condition of the patient could rapidly deteriorate because of the evolution of neurologic symptoms or because of complications of treatment, such as a hemorrhagic transformation of the infarct, necessitating urgent conversion from sedation to general anesthesia. Blood pressure manipulation, particularly induced hypertension, may be required to improve perfusion.[29]

Miscellaneous Uses

Clinicians have frequently used intracarotid drugs to treat life-threatening brain diseases, but the following applications of intracarotid drugs have not been widely recognized.

Intractable Increased ICP

Yokota *et al.*[170] used low-dose bilateral intracarotid infusion of mannitol to treat severely increased ICP in 18 human subjects with head trauma. They observed that intracarotid mannitol significantly decreased ICP and caused no hemodynamic side effects or disturbances in electrolyte status.

Severe Intracranial Infections

Medical treatment of purulent meningitis and encephalitis is sometimes complicated by the inability to deliver sufficient antibiotics to the infected site.[171] In experimental animals, intracarotid hyperosmolar disruption of BBB has been shown to enhance the delivery of tobramycin and vancomycin to the brain.[172] Even without hypertonic disruption, intracarotid antibiotics have yielded beneficial results in treating intracranial infections.[171,173–175]

Future Applications

Intraarterial Gene Therapy

Perhaps the most potent application of intracarotid drugs in the future is to deliver genes that could alter the course of a disease or help us to understand disease processes. Intracarotid delivery of viral vectors, DNA-bearing liposomes, and stem cells have all been successfully demonstrated.[176,177] Selective delivery of herpes viral vectors to tumor regions by concurrent use of Cereport (RMP-7) is one such example.[178] Bone marrow

stem cells have been successfully delivered to traumatized regions of the brain after intracarotid injection.[179] Although the field of gene therapy is in its infancy, intracarotid gene delivery could play a key role in the future treatment of brain diseases due to degeneration, ischemia, trauma, or neoplasia. Therefore, intracarotid drug delivery promises to play a critical role in emerging areas of molecular and restorative neurosurgery.[180,181]

Conclusions

During the past decade, compared with the technical advances in endovascular surgery, the field of intracarotid drug therapies has remained relatively ignored. There are ample anecdotal data to suggest that intracarotid drug therapy is effective for cerebral vasospasm, thromboembolic strokes, and neoplasms. However, there have been few attempts to systematically understand the kinetics of intracarotid drugs. The major efforts to deliver drugs selectively to the brain in the past decade have relied on molecular techniques to selectively penetrate the BBB (fig. 17). These advances in brain tissue drug targeting by novel neuropharmaceuticals come at a time of rapid advances in endovascular techniques, material sciences, and brain imaging that compel us to reevaluate intracarotid drug delivery. Intracarotid drug delivery can instantaneously generate exceedingly high local concentrations of the novel neuropharmaceuticals and thereby assist their regional delivery. Intracarotid drug delivery might be the primary route of drug delivery, or it could be used in conjunction with other brain tissue targeting technologies. Therefore, it is time to better understand the kinetics of intracarotid drugs and to develop techniques that could enhance the safety and reliability of such infusions.

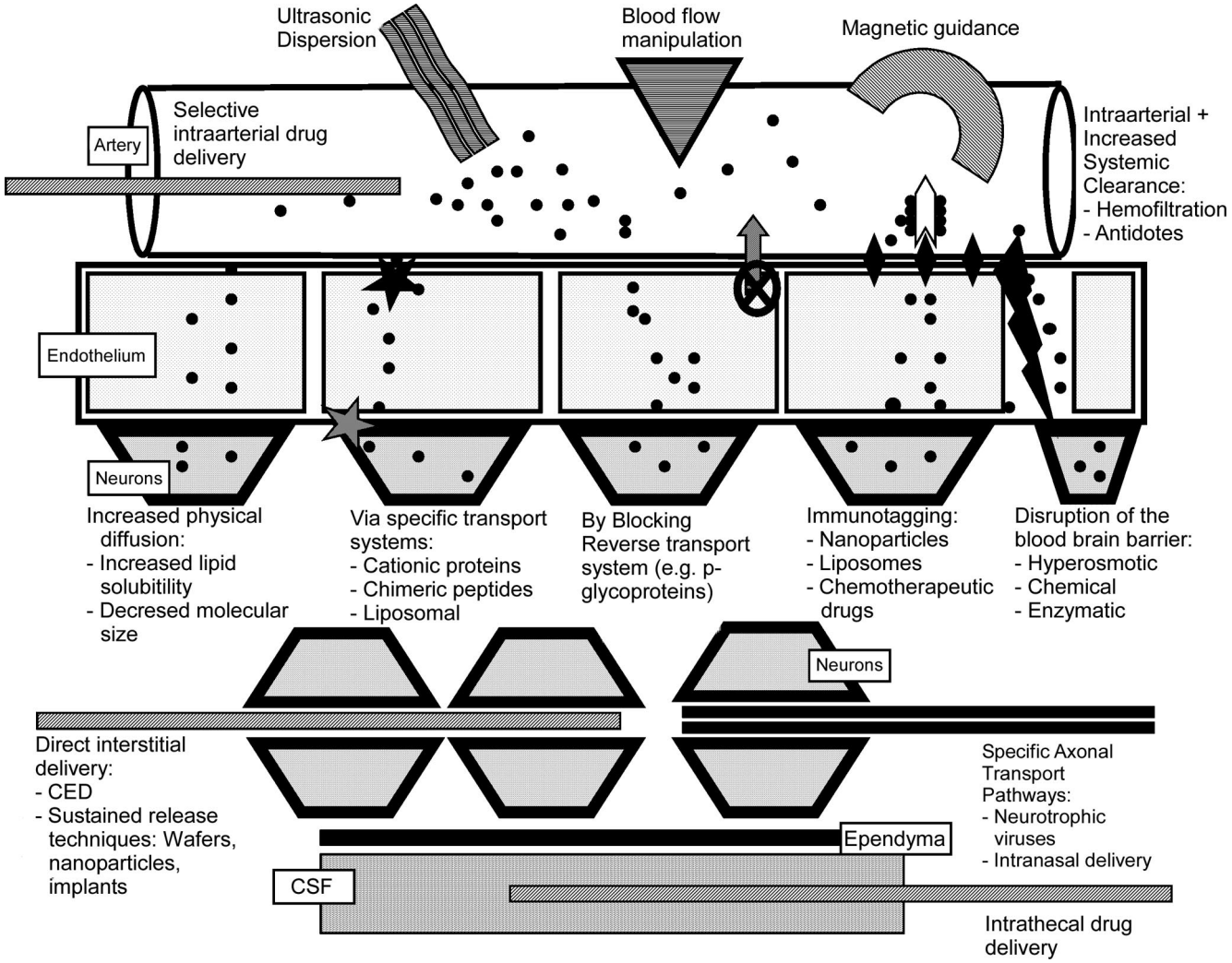

Fig. 17. Techniques of selective delivery of drugs to the brain that are currently under development. These techniques generally target unique features of the blood–brain barrier, such as specific molecules or transport mechanisms. Intracarotid delivery can enhance the effectiveness of these techniques by increasing the speed of onset of drug effects and delivering exceedingly high first-pass concentrations. CED = convection enhanced delivery; CSF = cerebrospinal fluid. From Joshi *et al.*[11]; used with kind permission of Springer Science and Business Media.

This review is dedicated to our parents, who, despite their hardships, always encouraged us to pursue our dreams. Acknowledgements are due to Mei Wang, M.P.H. (Staff Researcher, Department of Anesthesiology, Columbia University, New York, New York), for her help in preparing this manuscript and the ongoing intracarotid research, and Edward A. Neuwelt, M.D. (Professor of Neurology and Neurosurgery, Oregon Health and Science University, Portland, Oregon), for his help with illustrating this review (fig. 14).

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