AJNR

The Case for a Phase III Trial of Cerebral Intraarterial Fibrinolysis

Gregory J. del Zoppo, Randall T. Higashida and Anthony J. Furlan

AJNR Am J Neuroradiol 1994, 15 (7) 1217-1222
http://www.ajnr.org/content/15/7/1217.citation

Commentary

The Case for a Phase III Trial of Cerebral Intraarterial Fibrinolysis

Gregory J. del Zoppo, *Department of Molecular and Experimental Medicine, The Scripps Research Institute, and Division of Hematology/Medical Oncology, Scripps Clinic and Research Foundation, La Jolla, Calif*
Randall T. Higashida, *Departments of Radiology and Neurological Surgery, University of California, San Francisco Medical Center*
Anthony J. Furlan, *Department of Neurology, The Cleveland (Ohio) Clinic*

Brain infarction is common and costly and has no proved medical treatment. During the past decade, important advances in the pathophysiology of ischemic stroke, in imaging the brain, in fibrinolytic drugs and neuron-protecting agents, and in interventional neurovascular techniques have led to an increased awareness that therapeutic options now may be available to treat the previously untreatable causes and effects of acute stroke. It is evident, conceptually at least, that early recanalization of an occluded symptom-causing cerebral artery is a central strategy for improvement in clinical outcome. Although intuitively beneficial, cerebrovascular recanalization, whether by systemic or directed intraarterial infusion of a fibrinolytic agent, has yet to achieve the status of a proved therapy.

In the absence of firm data, speculation about the optimal strategy for clinical improvement through the delivery of a fibrinolytic agent abounds. Given the potentially serious (and even unknown) risks, any form of thrombolytic intervention for cerebral ischemia must be carefully and critically examined. In this issue of the *AJNR,* the Drs Ferguson (1) recognize this important caution. Among a number of issues raised in their paper about the efficacy of directed intraarterial delivery of a fibrinolytic agent, several demand closer scrutiny: (*a*) Does cerebral arterial recanalization translate into meaningful clinical improvement? (*b*) Is fibrinolysis safe? (*c*) At the current state of local intraarterial catheter technology, would experience with local intraarterial delivery of fibrinolytic agents be best collected by a registry or a phase III clinical trial approach? (*d*) Is it ethical to study a yet unproved invasive procedure without first collecting "experience" with it?

We wish to examine each of these issues more thoroughly in the context of directed superselective catheter application of fibrinolysis at the current state of catheter technology, plasminogen activator pharmacology, and accepted study design.

It is important to emphasize that studies designed to evaluate local intraarterial cerebral fibrinolysis are unique, because three important factors are concurrently being evaluated. The first is the technical component of the study design: the technique(s) required for drug administration. The second is the safety of the drug and optimal dose for recanalization. The third is the clinical efficacy of the treatment.

Recanalization and Clinical Outcome

Few trials of thrombus lysis in acute ischemic stroke (within 6 to 8 hours of symptom onset) would satisfy the accepted definition of phase III design (2). With the exception of two recent placebo-controlled studies of recombinant tissue plasminogen activator (alteplase and duteplase) delivered intravenously (3, 4), all reported experiences, whether based on intraarterial delivery (5–11) or on intravenous delivery (12–16) approaches, have been of type V according to the "rules of evidence" classification of Sackett (2, 17). That is, they lack any control group. Since the report by Clarke and Clifton in 1960 (18), the application of fibrinolytic techniques to stroke has been frozen in the "anecdotal" mode, a fate similar to cytoreductive therapy trials in oncology until a more formal approach to therapy testing was applied. Nonetheless, a metaanalysis of limited controlled experience with fibrinolysis in stroke has suggested clinical efficacy (19). But, Warlow

Address reprint requests to Gregory J. del Zoppo, MD, The Scripps Research Institute, 10666 N Torrey Pines Rd, La Jolla, CA 92037.
Index terms: Thrombolysis; Brain, infarction; Drugs, intraarterial injection; Interventional neuroradiology; Commentaries

AJNR 15:1217–1222, Aug 1994 0195-6108/94/1507–1217

and colleagues concluded that "thrombolysis for acute ischemic stroke deserves large and methodologically sound trials designed to answer a simple question: Does it work?" (19). Others have noted that controlled clinical trials in cerebrovascular disease are necessary and that "a return to clinical impressions would be completely unacceptable" (20).

In the last decade, reports of intraarterial delivery of urokinase or streptokinase locally (5, 6, 8–11) or regionally (17) have demonstrated the feasibility and relative safety of catheter application of the plasminogen activator. But the delivery systems available (eg, diagnostic catheters, controlled-leak balloons, and early microcatheter systems) were technically difficult to use. Pharmacologic recanalization by catheter-directed thrombus lysis was thus intricately tied to the delivery system for purposes of accessing the site of occlusion, as were the potential risks.

During that period the novel plasminogen activators recombinant tissue plasminogen activator (rt-PA) and single-chain urokinase plasminogen activator (scu-PA) were introduced. Their thrombus-selective properties (and the demonstration of successful recanalization of coronary arteries during the acute stage of myocardial infarction) were taken as a rationale for intravenous delivery and implied potential success in acute ischemic stroke. Two acute cerebral ischemia trial design approaches, implemented contemporaneously, took differing views of the need for vascular diagnosis in the study of intravenous plasminogen activators. To date, few of the effects of trials in which vascular diagnosis was used have survived: one phase I trial (of duteplase) was terminated when the sponsor lost a patent suit (12); a second recent phase I trial (of alteplase) was aborted without explanation; and a third study (of alteplase) was uncontrolled (14), leaving only the two placebo-controlled trials noted above as important guideposts (3, 4). Those prospective, hypothesis-driven trials have served to define relevant features of study design (including appropriate *clinical* inclusion and exclusion criteria), to refine the features of hemorrhagic transformation, and to demonstrate the feasibility of recanalization in the early hours of thrombotic/thromboembolic stroke. In the process, neurologic-outcome instruments were tested. Among the nonangiographic studies a number of pilot forays into clinical outcome were undertaken (15, 16), which, although not perfect, were very useful examinations of the safety of intravenous thrombolysis in the acute setting. The concept of functional outcome (with mortality) as a less subjective means of assessing benefit from the intervention is now being examined as part of several well-designed level I and II phase III trials of alteplase in acute ischemic stroke.

Although a direct comparison is yet to be made, it would seem that the frequency of recanalization achieved by intraarterial approaches so far tested (7, 11) is superior to that by intravenous approaches (3, 4, 12–16), although factors such as dose rate, timing, and observation techniques were not optimized in those angiography-based studies. This has reintroduced the question of whether intraarterial infusion of plasminogen activators could benefit patients (ie, improve their clinical outcome).

The Safety of Contemporary Intraarterial Infusion Techniques

The question of the risks attending the use of fibrinolytic agents in acute ischemic stroke is a central and complex one. The overall risks include those of the plasminogen activator (which may depend on the underlying injury, agent, dose rate, timing relative to the initial insult, vascular territory, and other factors) and those associated with the delivery system (including operator competence, the need for manipulation within the vasculature, and the state of the vasculature [eg, atheromatous lesions, artery tortuosity]).

Intravenous plasminogen activator studies have helped define the risk of the agent's producing intracerebral hemorrhage. A composite of studies suggests that hemorrhagic transformation is greater with late treatment (12), and increased dose rate (15, 21) (although this is disputed [12]). The incidence of hemorrhagic transformation in the setting of recent intravenous alteplase infusion for documented acute embolic stroke has not been substantially different from placebo controls (3, 13, 22) or literature reports (12, 14). There are anecdotal reports that coexistent hypertension may contribute to intracerebral hemorrhage in the setting of fibrinolysis (21). It also has been suggested that the angiographic procedure per se may be directly causative, but no experience has been reported to support this claim.

In terms of the delivery system, an intravenous infusion presents less of a risk to the

patient than superselective catheter placement in the intracranial circulation. But the risks of direct cerebral intraarterial, microcatheter-mediated delivery systems are not completely known. From experience in other arterial territories including the coronary, femoral, iliac, and distal peripheral arteries, the reported risks are low. For directed delivery of any agent into the cerebral arterial circulation, two procedures are required: cerebral angiography and an interventional technique.

Cerebral angiography is critical to document the occlusion site, correlate it with clinical symptoms, and evaluate objectively the recanalization efficacy of the proposed treatment. The safety and efficacy of cerebral angiography is undisputed, and it is currently the standard to which all current imaging modalities are compared for evaluation (23). In 1978 Mani et al reported experience with 5000 patients studied by conventional catheter cerebral angiography over a 6-year period at four medical centers (two academic/training hospitals and two community/nontraining hospitals) (24–26). All patient records were analyzed and reviewed before, during, and for 48 hours after the cerebral angiogram, and all adverse events were recorded. They reported a total morbidity of 1.4%, with an incidence of permanent complications of only 0.1% and a mortality of only one patient (0.02%).

Other noninvasive methods have been evaluated to correlate anatomic information related to cerebrovascular disorders, including magnetic resonance angiography and imaging, computed tomography with three-dimensional vascular reconstruction techniques, transcranial Doppler scanning, and nuclear medicine blood flow imaging (27–31). Each of these has limitations ranging from objectivity of measurement (transcranial Doppler) to resolution (transcranial Doppler and magnetic resonance angiography), which make them currently unsuitable for use in prospective vascular or clinical outcome trials.

In addition to the risks of cerebral angiography there are also the potential complications of microcatheter manipulation and placement at the occlusion site. In 1986, microcatheters composed of soft 2.7-F polyethylene tubing became commercially available specifically to access the brain vessels in an atraumatic fashion. When combined with an 0.016-in steerable microguidewire, the distal intracranial branches above the skull base could be accessed with relative ease by the neurointerventionalist.

A number of reports have appeared from centers experienced in the use of microcatheter systems of this type that give a view of the safety of these techniques (32–39). Halbach and Higashida in 1991 reported a 5-year experience of 1200 interventional endovascular procedures using microcatheter systems in the central nervous system. Technique-related complications caused by placement of the microcatheter into the targeted blood vessel included 15 perforations and dissections of intracerebral blood vessels (1.25%). Those consisted of perforation of a normal vessel in 6 cases, disruption of a dysplastic vessel or aneurysm in 5 cases, and fluid over injection in 4 cases. There were two deaths and three long-term sequelae in this group, accounting for 5 (0.42%) permanent complications among the 1200 cases (40).

The ability to access safely the larger proximal vessels arising from the intracranial circulation, including the M1 and proximal M2 branches of the middle cerebral artery, and the distal vertebral and basilar arteries, is now being routinely performed in a safe and efficacious fashion at institutions currently performing interventional therapy. Access is everything to the interventional neuroradiologist: protocols enabling treatment of intracranial aneurysms using electrolytically detachable coils (available for the past 4 years), detachable balloons (for 8 years), and treatment of arteriovenous malformations and traumatic vascular injuries (for 9 years) in the proximal and distal cerebral arterial tree to fourth- and fifth-division arteries less than 1.0 mm in diameter have demonstrated the safety and efficacy of microcatheter devices and the access techniques (32, 33, 35, 36, 41, 42). The evaluation of these techniques in interventional neuroradiology would not be possible without the prerequisite of safe and attainable access to the target lesion by the microcatheter and guide wire systems currently in use.

There are additional considerations regarding the direct delivery of the microcatheter and the required expertise which are relevant to the issues of safety and efficacy. Microcatheter design, positioning of the microcatheter, and the delivery format are three variables that must be considered. The number of microcatheter delivery ports; the configuration of the hole(s),

whether the distal microcatheter tip is to be placed proximal to the occlusion, at the thrombus, or through it; and whether an agent is to be administered by continuous infusion or by pulse spray are only a small number of the numerous design variations that must be considered (38). In the absence of properly designed direct comparisons, it is not possible to determine rationally which variation is the most efficacious. A simple but relatively safe approach based on current interventional experience would be a rational starting point.

Who, then, should undertake these studies? To study the recanalization–clinical outcome question a number of centers are required. The choice of the technical procedure to use in a protocol involving multiple participating centers requires appropriate expertise and standardization of the procedure to minimize bias and the number of variables that may confound outcome interpretation. An easily overlooked consideration is the need to separate the effects of the catheterization from those of the plasminogen activator in early trials so that a treatment-safety baseline may be established. For intraarterial infusion techniques, individual center capability and expertise in the technical skills of performing the procedures may be judged by demonstrated experience in placing microcatheter systems safely to branch vessels, as during neurointerventional procedures, for instance. Here the learning curve already will have been ascended for the microcatheter delivery technique based on prior experience with other interventional protocols in the same vascular distribution.

Registry Versus Phase III Trials

The debate here is not whether it is appropriate to conduct a sophisticated phase III trial of the efficacy of intraarterial thrombolysis rather than a registry. There is no question that the safety of an identified approach first must be established, even in the face of anecdotal reports of clinical benefit. However, the use of databases, of which a registry is one, is ultimately inadequate for comparing treatment approaches from which sound inferences may be made "because of difficulties with bias in treatment assignment, nonstandard definitions, definitions changing in time, specifications of groups to be compared, missing data, and multiple comparisons" (43). One of the principal weaknesses of the registry approach in the current setting is that it is simply not feasible to evaluate all of the technical variables related to thrombolysis by the plethora of intraarterial techniques proposed.

Once one attempts to provide an experimental basis for modifying the techniques, statistical considerations demand a minimum common patient experience, and a phase I trial evolves. Each variation in technique (eg, catheter placed within or driven through the thrombus), medical device change, or modification of catheter-based materials therefore would require a new study for evaluation. When approached rationally it should be, and in other venues has been, possible to build successfully on experience obtained in an organized fashion.

The essential challenge here is how to approach rationally the question of clinical outcome in acute stroke using pharmaceutical recanalization techniques. Registry-founded approaches to the study design problem have the further limitation that there is inherently no control on which to base previous experience to prove the safety or efficacy of the techniques. To use the last patient treated as the control subject for the next patient lacks rationale and begs standardization.

It is therefore most reasonable to base a phase I clinical trial on a current acceptable standard of practice. In this setting, in the absence of other compelling data to the contrary, if the technique of embedding a single end-hole catheter directly into a short segment of thrombus has been shown to be efficacious in lysing the clot in other vascular territories with similar artery sizes, flow, and thrombus maturity, this logically could be the starting point for evaluation of more advanced techniques. Comparative studies based on modifications in evolved techniques could follow.

Appropriately designed phase I and phase II trials testing defined hypotheses must serve as the groundwork for further testing of the (refined) hypothesis in a controlled fashion by the phase III scheme. Alterations in technique, in hypothesis, or in study protocol are possible based on experience in a phase I or phase II trial. At the minimum, those accepted formats offer a logically sequenced paradigm to the formal testing of a defined question—in this instance, whether direct intraarterial infusion of a thrombolytic agent will improve the long-term clinical outcome of a patient treated in the acute

phase of a thrombotic or atherothromboembolic stroke.

Ethical Considerations

A registry is not a substitute for a phase III trial. It cannot address the ethical dilemmas of whether the approach in question is indeed not harmful to the patient, and it is also of no benefit. This can be determined only when properly defined controls are used for comparison with the test approach. A registry does not demand equipoise between approach A and the control approach or approach B.

The ethics of properly designed and conducted randomized trials are well established. Indeed, Friedman et al have argued that double-blind studies are *more* ethical than other studies because they provide better and more useful information and minimize the opportunities for bias (44). One aspect of many blinded trials, that of placebo control, can be ethically justified if there is no superior standard treatment, a clear situation in the treatment of acute cerebral ischemia. Here the informed consent should state clearly that a placebo will be given to some subjects, what the odds of receiving a placebo are, and the justification for its use (45).

Although the ethics of the randomized clinical trial design are widely accepted (46–49), preliminary data should provide reason to believe that the treatment under investigation is significantly better than standard therapy or, where none exists, the natural history of the disease process. Natural history, however, should not be used as a control but can serve to estimate sample size.

Obviously, the risks of therapy must be examined carefully and minimized. This is one purpose of a phase I trial. It is the ethical responsibility of the investigators to monitor data during a trial, both for early benefit or harmful side effects. Safety is best monitored independently from the trial using prospectively established limits. The use of control subjects and proper monitoring serve to safeguard patients in randomized trials, but no assurance is provided in uncontrolled trials or registries that explore technique. Indeed, without proper controls it may be impossible to know if a new treatment is helping or hurting patients with acute brain ischemia.

To return to an earlier point, one way to minimize risk is to maximize the quality of the centers participating in a randomized trial. Randomized trials are not the proper forum for learning a new technical skill. If centers that have acquired the experience to perform the central procedure with which the hypothesis is to be tested can be identified, then proper phase I and phase II trials may be contemplated. By selecting centers with not only interventional but also neurologic expertise and standardizing the treatment delivery system and entry criteria within a randomized, controlled design, not only will the most useful scientific information be obtained, but patient risk should be minimized.

Concern about the right moment to conduct controlled clinical trials for new and evolving technology or treatment modalities always will be present. However, without these objective studies, physicians may be locked into a treatment that may be of little benefit, or even harmful, based on anecdotal experience only. There is a pressing need to know whether local cerebral thrombolysis is safe and efficacious and significantly improves clinical outcome. By continuing the practice of uncontrolled anecdotal-experience case reporting without optimizing the technique, drug, and dose, we risk doing our patients and the practice of medicine a disservice.

References

1. Ferguson RDG, Ferguson JG. Cerebral intraarterial fibrinolysis at the crossroads: is a phase III trial advisable at this time? *AJNR Am J Neuroradiol* 1994;15:1201–1216
2. del Zoppo GJ. Antithrombotic therapy in cerebrovascular disease. In: Loscalzo J, Schafer AI, eds. *Thrombosis and Hemorrhage.* Boston: Blackwell Scientific Publications, 1994:1225–1252
3. Mori E, Yoneda Y, Tabuchi M, et al. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology* 1992;42:976–982
4. Yamaguchi T, Hayakawa T, Kiuchi H. Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke. *Cerebrovasc Dis* 1993;3:269–272
5. Zeumer H, Hundgen R, Ferbert A, Ringelstein EB. Local intraarterial fibrinolytic therapy in inaccessible internal carotid occlusion. *Neuroradiology* 1984;26:315–317
6. del Zoppo GJ, Ferbert A, Otis S, et al. Local intra-arterial fibrinolytic therapy in acute carotid territory stroke: a pilot study. *Stroke* 1988;19:307–313
7. Mori E, Tabuchi M, Yoshida T, Yamadori A. Intracarotid urokinase with thromboembolic occlusion of the middle cerebral artery. *Stroke* 1988;19:802–812
8. Theron J, Courtheoux P, Casaseo A, et al. Local intraarterial fibrinolysis in the carotid territory. *AJNR Am J Neuroradiol* 1989; 10:753–765

9. Zeumer H, Hacke W, Ringelstein EB. Local intraarterial thrombolysis in vertebrobasilar thromboembolic disease. *AJNR Am J Neuroradiol* 1983;4:401–404
10. Hacke W, Zeumer H, Ferbert A, Brückmann H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. *Stroke* 1988;19:1216–1222
11. Matsumoto K, Satoh K. Topical intraarterial urokinase infusion for acute stroke. In: Hacke W, del Zoppo GJ, Hirschberg M, eds. *Thrombolytic Therapy in Acute Ischemic Stroke.* Heidelberg: Springer-Verlag, 1991:207–212
12. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32:78–86
13. Yamaguchi T. Intravenous tissue plasminogen activator in acute thromboembolic stroke: a placebo-controlled, double-blind trial. In: del Zoppo GJ, Mori E, Hacke W, eds. *Thrombolytic Therapy in Acute Ischemic Stroke II.* Heidelberg: Springer-Verlag, 1993: 59–65
14. von Kummer R, Hacke W. Safety and efficacy of intravenous tissue plasminogen activator and heparin in acute middle cerebral artery. *Stroke* 1992;23:646–652
15. Brott TG, Haley EC Jr, Levy DE, et al. Urgent therapy for stroke, I: pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke* 1992;23:632–640
16. Haley EC Jr, Levy DE, Brott TG, et al. Urgent therapy for stroke, II: pilot study of tissue plasminogen activator administered 91–180 minutes from onset. *Stroke* 1992;23:641–645
17. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1983;89 (suppl):2S–3S
18. Clarke RL, Cliffton EE. The treatment of cerebrovascular thrombosis and embolism with fibrinolytic agents. *Am J Cardiol* 1960; 30:546–551
19. Wardlaw JM, Warlow CP. Thrombolysis in acute ischemic stroke: does it work? *Stroke* 1992;23:1826–1839
20. Hachinski V. Multicenter trials in stroke. *Arch Neurol* 1990;47:445
21. Levy DE, Brott TG, Haley EC Jr, et al. Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. *Stroke* 1994;25: 291–297
22. Mondino BJ, Brady KJ. Distribution of hemolytic complement in the normal cornea. *Arch Ophthalmol* 1981;99:1430
23. Osborn AG. Technical aspects of cerebral angiography. In: *Introduction to Cerebral Angiography.* Philadelphia: Harper & Row, 1980:1–31
24. Mani RL, Eisenberg RL, McDonald EJ, Pollock JA, Mani JR. Complications of catheter cerebral arteriography: analysis of 5000 procedures, I: criteria and incidence. *AJR Am J Roentgenol* 1978;131:861–865
25. Mani RL, Eisenberg RL. Complications of catheter cerebral arteriography: analysis of 5000 procedures, II: relation of complication rates to clinical and arteriographic diagnosis. *AJR Am J Roentgenol* 1978;131:867–869
26. Mani RL, Eisenberg RL, McDonald EJ, Pollock JA, Mani JR. Complications of catheter cerebral arteriography: analysis of 5000 procedures, III: assessment of arteries injected, contrast medium used, duration of procedure, and age of patient. *AJR Am J Roentgenol* 1978;131:871–874
27. Baker LL, Kucharczyk J, Sevick RJ, Mintorovitch J, Moseley ME. Recent advances in MR imaging/spectroscopy of cerebral ischemia. *AJR Am J Roentgenol* 1991;156:1133–1143
28. Lewis JS, Laub G. Intracranial MR angiography. A direct comparison of three time of flight techniques. *AJNR Am J Neuroradiol* 1991;12:1133–1139
29. Masaryk TJ, Modic MT, Ross JS, et al. Intracranial circulation: preliminary clinical results with three dimensional (volume) MR angiography. *Radiology* 1989;171:793–799
30. Crosby DL, Turski PA, Davis WL. Magnetic resonance angiography and stroke. *Neuroimaging Clin N Am* 1992;2:509–531
31. Caroll BA. Carotid sonography. *Neuroimaging Clin N Am* 1992; 2:533–557
32. Vinuela F. Functional evaluation and embolization of intracranial arteriovenous malformations. In: Vinuela F, Halbach VV, Dion J, eds. *Interventional Neuroradiology: Endovascular Therapy of the Central Nervous System.* New York: Raven Press, 1992:77–86
33. Halbach VV, Higashida RT, Barnwell SL, Dowd CF, Hieshima GB. Transarterial platinum coil embolization of carotid cavernous fistulas. *AJNR Am J Neuroradiol* 1991;12:429–434
34. Higashida RT, Hieshima GB, Halbach VV. Advances in the treatment of complex cerebrovascular disorders by interventional neurovascular techniques. *Circulation* 1991;83:I196–I206
35. Higashida RT, Halbach VV, Tsai FY, et al. Interventional neurovascular treatment of traumatic carotid and vertebral artery lesions: therapeutic results in 234 cases. *AJR Am J Roentgenol* 1989;153:577–582
36. Halbach VV, Higashida RT, Hieshima GB, Hardin CW. Embolization of branches arising from the cavernous portion of the internal carotid artery. *AJNR Am J Neuroradiol* 1989;10:143–150
37. Dion JE. Principles and methodology. In: Vinuela F, Halbach VV, Dion J, eds. *Interventional Neuroradiology: Endovascular Therapy of the Central Nervous System.* New York: Raven Press, 1992:1–16
38. Lasjaunias P, Berenstein A. *Surgical Neuroangiography. Functional Anatomy of Craniofacial Arteries.* Berlin: Springer Verlag, 1987
39. Tsai FY, Higashida RT. Intravascular therapeutic embolization of acute traumatic vascular lesions of the head and neck. In: Neal MP, Tisnado J, Cho S, eds. *Emergency Interventional Radiology.* Boston: Little, Brown and Co, 1989:369–384
40. Halbach VV, Higashida RT, Dowd CF, Barnwell SL, Hieshima GB. Management of vascular perforations that occur during neurointerventional procedures. *AJNR Am J Neuroradiol* 1991;12:319–328
41. Higashida RT, Halbach VV, Dowd CF, Barnwell SL, Hieshima GB. Intracranial aneurysms: interventional neurovascular treatment with detachable balloons: results in 215 cases. *Radiology* 1991; 178:663–670
42. Guglielmi G. Embolization of intracranial aneurysms with detachable coils and electrothrombosis. In: Vinuela F, Halbach VV, Dion J, eds. *Interventional Neuroradiology: Endovascular Therapy of the Central Nervous System.* New York: Raven Press, 1992:63–75
43. Byar DP. Why data bases should not replace randomized clinical trials. *Biometrics* 1980;36:337–342
44. Friedman LM, Furberg CD, De Mets DL. Blindness. In: *Fundamentals of Clinical Trials.* 2nd ed. Littleton, Mass: PSG Publishing Co, 1985:71–81
45. Bok S. The ethics of giving placebo. *Sci Am* 1974;23I:17–23
46. Schafer A. The ethics of the randomized clinical trial. *N Engl J Med* 1982;307:719–724
47. Burkhardt R, Kienle G. Controlled clinical trials and medical ethics. *Lancet* 1978;ii:1356–1359
48. Shaw LW, Chalmers TC. Ethics in cooperative clinical trials. *Ann NY Acad Sci* 1970;169:487–495
49. Wilhelmsen L. Ethics of clinical trials: the use of placebo (editorial). *Eur J Clin Pharmacol* 1979;16:295–297