Getting It Right the First Time

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In this issue of the AJNR, Theron et al. [1] report on a retrospective analysis of carotid angioplasty in 13 patients in whom a modification of a previously described catheter system designed to protect the cerebral circulation during the procedure was used. The temporary arrest of flow within the internal carotid artery and flushing of the arterial segment proximal to the temporary occlusion balloon are key technical elements. Selection criteria for patients included a history of transient ischemic attacks or stroke (10 patients) and history of no augmentation in cerebral blood flow after acetazolamide challenge in cerebral blood flow analysis (three asymptomatic patients). Restoration of hemodynamic normalcy occurred in all but one patient, as inferred from the degree of residual stenosis seen on angiography and findings on postprocedure carotid Doppler studies. All patients received either aspirin or ticlopidine before the procedure and for 2 months after angioplasty. The authors also describe a variation of their standard procedure in the treatment of lesions involving adjacent segments of both the internal and common carotid arteries. No procedural complications occurred, and all patients had no new or recurrent symptoms during a mean follow-up period of 8.5 months.

Theron et al. conclude that their catheter system offers several advantages over other systems. They also theorize that angioplasty may promote healing of ulcerative lesions; therefore, patients who have such lesions should not be excluded from angioplasty therapy. The authors also assert that nonaugmentation in cerebral blood flow after acetazolamide challenge is a justifiable basis for selection of asymptomatic patients for carotid angioplasty.

In addition to the methodologic limitations of any retrospective study, several issues, including criteria for selection of patients, follow-up, possible alternative therapies, and assertions about the action and effectiveness of the authors’ cerebral protection system, deserve further consideration. With regard to the selection criteria, the inclusion of asymptomatic patients warrants comment. The fortuitous finding of carotid stenoses discovered in the course of angiographic investigations for multiple atherosclerotic lesions apparently prompted the authors to ask their subjects to submit to a cerebral blood flow analysis with acetazolamide challenge. On the basis of that test, some patients were offered a prophylactic therapeutic procedure. The logical basis for such a therapeutic algorithm deserves closer scrutiny. The authors cite the work of Rogg et al. [2] to justify treatment of asymptomatic carotid stenosis by angioplasty or surgery, if the patients have shown no augmentation in cerebral blood flow after acetazolamide challenge. Although it seems reasonable that such patients may be at risk for hemodynamic insufficiency, the magnitude of that risk has never been established. It would be purely speculative to assert that this unknown risk is greater or less than the risk of carotid angioplasty, particularly when the risks of the latter procedure are not fully known. Furthermore, even if the procedural risks of angioplasty were known, no statistically significant data are available to substantiate the claim that carotid angioplasty is of value in preventing the clinically significant end points of stroke and death. In this regard, it appears that Theron et al. may be using assumptions to justify assumptions, which in turn are used to justify further assumptions. The methodological soundness of such a practice is at best questionable. Also, although acknowledging the effectiveness of platelet antiaggregants such as ticlopidine in reducing the risk of clot emboli, Theron et al. did not discuss the merits of a preangio-

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plasty therapeutic trial with these agents as one possible alternative to angioplasty. It is for these reasons that restriction of this procedure to surgically inaccessible lesions in symptomatic patients, possibly after unsuccessful medical therapy, would seem advisable.

Other methodological questions left unanswered include (1) What was the basis for assignment of patients to angioplasty rather than to the more traditional and accepted form of revascularization procedure: carotid endarterectomy? (2) Was angioplastic treatment of carotid lesions restricted to those ipsilateral to the affected hemisphere? (3) Were any binding techniques used in data analysis?

The absence of recurrence of neurologic symptoms in the subjects over a mean follow-up period of 8.5 months is encouraging. If indeed the patients were deprived of platelet antiaggregate medication after 2 months, this would seem to remove that variable as a possible factor in the prevention of recurrent symptomatology, as these medications are known to confer protection against transient ischemic attacks and stroke. I am uncertain, however, how to resolve the apparent ethical dilemma of denying the patients the scientifically validated benefits of this type of medication for the sake of methodological clarity.

The absence of recurrent symptoms, at least in some patients in this series, might be due to chance alone. This is not an unreasonable assumption; the most important clinical end points tend to fluctuate with time, independent of intervention [3]. It might have been enlightening to include an estimate of the expected event rate, if feasible.

Finally, with regard to the follow-up of the asymptomatic patients, Theron et al. report “a marked subjective clinical improvement” in the three asymptomatic patients. This is particularly troubling given the absence of symptoms before treatment. I am left to ponder what clinical entity must have been present originally to have undergone marked improvement subsequently.

Central to the authors’ thesis is the issue of iatrogenic embolization related to the performance of carotid angioplasty. The finding of cholesterol crystals in four (67%) of six samples suggests that carotid angioplasty without “cerebral protection” might be expected to result in a high rate of neurologic complications if, indeed, distal embolization is a valid surrogate end point for the more clinically significant end points of stroke and death. This, however, has not been observed in other carotid angioplasty procedures performed without cerebral protection, in which the complication rate was nowhere near that which would be predicted by the aforementioned sampling result [4]. Clearly, if embolization of cholesterol crystals occurs as frequently as is suggested by the series of Theron et al. either the brain frequently tolerates such embolic material, or alternatively, the damage produced by such events must elude detection because of observer error or poor study design. These two possibilities deserve further consideration.

Numerous examples of inadvertent iatrogenic embolization in the cerebral vasculature exist, and most frequently are the result of endovascular therapeutic procedures gone awry. Many interventionalists have had the disquieting experience of producing a variety of errant emboli, including such items as silicone spheres, latex balloons, gold marker beads, platinum microcoils, and, occasionally, portions of cerebral catheters. It is truly amazing (and relieving) to see how often the brain is able to tolerate such insults. It is perhaps a tribute not only to the plurality of collateral vascular pathways but also probably to the resiliency of the brain that such mishaps are not associated inevitably with disaster. In any event, one thing appears certain: emboli seen on angiograms are not invariably associated with an adverse clinical neurologic outcome. That said, the absence of an adverse clinical outcome does not, therefore, exclude the possibility of either nonvisualized or angiographically visualized emboli. If understanding of such complex and unexpected clinical and angiographic relationships is to be forthcoming, we first must attempt to optimize detection of these occurrences. In this regard, Theron et al. have failed to inform us of their attempts to scrutinize the postangioplasty angiogram for evidence of distal emboli that might have eluded their protective system. Yet they give legitimacy to this very concern by their own statement that “most” emboli are prevented from reaching the cerebral circulation. If not conjecture, this seems to imply that they may have some evidence for iatrogenic cerebral emboli, despite their protective catheter system.

On the other hand, serious damage to the brain may occur without angiographically recognizable abnormalities. Therefore, a normal postprocedure angiogram does not exclude an iatrogenic stroke because even permanent damage to the brain may not always be recognized easily. The importance of this point was underscored by the work of Brott and Thalinger [5], who found that stroke immediately after endarterectomy was underreported because the surgical service failed to recognize the adverse neurologic event. Any precautions against similar errors have not been documented by Theron et al., who have failed to provide details of the method of immediate and longer term clinical neurologic follow-up.

With regard to the actual technique used by Theron et al. in the performance of cerebral angioplasty, the addition of two extra catheters as compared with a standard angioplasty system does appear to offer several positive benefits. These benefits, however, come at a price. In addition to procedural ease and efficiency, even some elements of safety conceivably might be compromised. Specific concerns involve the placement of a large, relatively stiff introducer catheter, which may be difficult and, in some cases, impossible, in the tortuous vessels of an elderly hypertensive patient. At a minimum, it will add complexity to the procedure and, in addition, may be an added source of catheter-related complications.

A more serious concern relates to the use of the 3-French latex occlusion balloon system. The requirements for passage of a second device across a tight stenosis, in addition to the angioplasty catheter, seem to be incredibly demanding, particularly given the inherent inferiority of a latex balloon tip catheter to act as either a probe or a dilator as compared with a guidewire. My colleagues and I occasionally have had considerable difficulty passing even a small guidewire (0.012–0.035 in. [0.3–0.9 mm]). Any difficulty could only be compounded by the additional requirement of passing both the
angioplasty guidewire and the latex occlusion balloon system in parallel. I have little doubt that this system would be unworkable in the hands of most physicians attempting to treat a near occlusion. It would be interesting to know if Theron et al. were unsuccessful in the attempted treatment of patients not in this series. Finally, it seems logical that the additional, more complicated instrumentation of the stenosis also might result in a higher rate of local complications at the site of the lesion, possibly related to dissection or disruption of plaque. Although I think that the principle of flow arrest in the target artery is an excellent one, I think it may be applied through a different technical approach: using a double-lumen occlusion introducer catheter and providing flow arrest in the target artery by a placement proximal to the lesion. Such a system eliminates the need for passage of a second device in parallel across the lesion while providing an outlet for any particles by taking advantage of the natural backflow of blood through the catheter.

In conclusion, this valiant search for an angioplasty system, designed to limit distal emboli, is a worthy one. A rigorous approach to the evaluation of the technical merits of the system, while mandatory, is insufficient as, ultimately, the occurrence of distal emboli does not appear to be directly related to the development of clinically significant neurologic change. The relationship between iatrogenic emboli and neurologic effect remains to be defined more clearly.

As important in carotid angioplasty as the technique itself is the design of any study or trial used to assess the value of the procedure as a valid therapeutic option for the prevention of stroke and death. This requires the establishment of rational selection criteria and a vigilant and compulsive approach to data collection and analysis. In this regard, we must look for assistance from methodologists, biostatisticians, and epidemiologists. We also must be prepared to collaborate more with clinical neuroscientists, particularly in the field of stroke neurology. Our techniques must be above reproach both in and outside the angiography suite. This is an opportunity not only to provide a potentially superior form of revascularization therapy but also to expand the horizons of neurovascular physiology. The application of rigorous principles for scientific study may enable us to get it right the first time this time.

REFERENCES