Cerebral Angiographic Risk in Mild Cerebrovascular Disease

Graeme J. Hankey, MBBS, FRACP, Charles P. Warlow, MD, FRCP, and Robin J. Sellar, MBBS, BSc, MRCP, FRCR

We review the eight prospective and seven retrospective studies from which it is possible to derive the complication rate of conventional cerebral angiography for patients with mild ischemic cerebrovascular disease who are potential candidates for carotid endarterectomy. Three studies of intravenous and one of intra-arterial digital subtraction angiography are also examined. An overview of the results suggests that the risk of a neurological complication (TIA or stroke) is about 4% and that a permanent neurological deficit (disabling stroke) occurs in about 1%. The mortality rate is very low (<0.1%). Systemic complications are not infrequent, particularly with intravenous digital subtraction angiography. The complication rate of cerebral angiography must be considered when evaluating the risks of carotid endarterectomy in patients with ischemic cerebrovascular disease. (Stroke 1990;21:209-222)

The management of cerebrovascular disease is concerned as much with the prevention as with the management of acute stroke, particularly when the stroke is mild. Potential preventive measures include the management of vascular risk factors and the use of antiplatelet agents, anticoagulant therapy, and carotid endarterectomy. No randomized trials have adequately addressed the utility of carotid endarterectomy, but several are in progress in western Europe and North America. We hope that these trials will provide sufficient information for a rational decision to be made as to whether carotid endarterectomy improves the stroke-free survival of patients with transient ischemic attacks (TIAs) or mild ischemic stroke in the carotid artery distribution and patients with asymptomatic carotid stenosis. If they do, then we will need to know the risks of the necessary preoperative investigations that would not otherwise be done in normal clinical practice, particularly cerebral angiography.

Before undertaking carotid endarterectomy, it is essential to visualize any surgically accessible stenotic or ulcerative lesion at the symptomatic carotid bifurcation. Many surgeons also want to know if there is proximal disease in the aortic arch or carotid system, severe distal disease in the carotid siphon (which may preclude carotid endarterectomy), and disease on the opposite side.

The extracranial carotid arteries can be visualized noninvasively using ultrasound duplex imaging and invasively using either intravenous (IV) or intra-arterial (IA) digital subtraction angiography (DSA) or conventional cerebral angiography. Although carotid endarterectomy is occasionally performed on the basis of ultrasound studies alone,1 almost all surgeons require angiographic demonstration of the extracranial carotid arteries before considering carotid endarterectomy and, in the United Kingdom at least, the vast majority of surgeons prefer selective intra-arterial cerebral angiography.2

Noninvasive studies can be highly accurate in the initial evaluation of a patient with carotid artery disease, but noninvasive studies do not visualize the proximal or distal carotid circulation and considerable difficulty may be encountered in distinguishing high-grade stenosis from complete occlusion of the internal carotid artery (ICA). This distinction is important because the management of high-grade stenosis differs from that of complete ICA occlusion.3 IV-DSA can be regarded as only a screening tool because it is simply too inaccurate and because only approximately 80% of the studies are likely to be interpretable.4-6 It is generally accepted that biplane cerebral angiography or IA-DSA is essential to confirm the presence of complete ICA occlusion7,8 and that selective biplane intra-arterial cerebral angiography with suitable subtraction imaging is the most accurate means of evaluating both the extracranial and the intracranial cerebrovascular systems,3,5 although Jeans et al9 have shown that triplane cere-
bral angiography can often be even more accurate. The newer imaging modalities (duplex imaging, IV-DSA) have been developed not because they are more accurate than selective cerebral angiography (they are not) but because there are several drawbacks to conventional cerebral angiography (the needs for hospitalization and, in some centers, for general anesthesia, patient discomfort, cost, and a small but definite risk of permanent complications or even death).

**What Is the Risk of Cerebral Angiography in Patients With TIA and Minor Ischemic Stroke?**

Although it is well recognized that there is an inherent risk in conventional cerebral angiography, the degree of risk is uncertain, as it is with DSA, and reports of the risk vary considerably, from as low as 0% to as high as 28% among the many studies addressing this issue. These inconsistent results reflect the heterogeneity of the studies, particularly in terms of study design, patient selection, sampling errors, angiographic technique and procedure, and the definition, assessment, and interpretation of complications and outcome.

Almost all the early studies were retrospective. The problems of such studies are both administrative (clinical notes or crucial data missing) and methodologic (haphazard patient selection, nonstandard diagnostic and outcome criteria, variation in follow-up frequency, and bias due to nonblinded reviewers). Prospective accumulation of data is a more sensitive method of investigation that permits the notification of "minor" but nonetheless distressing complications that may go undetected in a retrospective study.

In many early studies, the type of patient studied was one with a completed stroke; few, if any, patients had TIAs. In other studies, the category "cerebrovascular disease" was used without further subdivision. It is important to be more specific because complication rates may differ for patients with different forms of cerebrovascular disease.

Different angiographic techniques have been used over the years, and in early studies a high incidence of complications was recorded after percutaneous carotid puncture. This high complication rate was ascribed to dislodgement of atherosclerotic plaque by the needle. Later, it was believed that improved catheter techniques would largely end the problem of cerebral complications, but this has clearly not happened. The complication rate for cerebral angiography depends heavily on the definition of complications and on the thoroughness of postangiographic observation, both of which also vary considerably among studies. Hence, many comparisons of studies relating to the complications of cerebral angiography may not be valid.

To obtain the most accurate information concerning the preoperative risk of conventional cerebral angiography for patients with TIA or mild ischemic stroke who are being considered for carotid endarterectomy, which can be validly compared, it is necessary to select carefully from the available literature those studies that used consistent and sound methodology and analysis. We think that the following criteria should be adhered to, although not all of them have been fulfilled in any published study:

1. The data are prospectively accumulated in consecutive patients.
2. The type of patient studied is defined, and patients with TIAs or mild ischemic stroke who are suitable candidates for carotid endarterectomy are studied. TIA is defined as an acute loss of focal cerebral or ocular function with symptoms lasting <24 hours and which after adequate investigation is presumed to be due to embolic or thrombotic vascular disease, and stroke is defined as rapidly developing symptoms and/or signs of focal, and at times global (applied to patients in deep coma and those with subarachnoid hemorrhage), loss of cerebral function with symptoms lasting >24 hours or leading to death, with no apparent cause other than one of vascular origin. Stroke is considered minor if neurologic symptoms resolve within 1 week and major if symptoms last ≥1 week. Strokes can be further subclassified as either nondisabling or disabling.
3. The date of onset of the last TIA or stroke is recorded.
4. The type of angiographic procedure performed (aortic arch and/or selective carotid angiography via the transfemoral or direct carotid route, IA-DSA, or IV-DSA) is defined.
5. The type of contrast medium used is defined.
6. The angiographer (an experienced consultant neuroradiologist or a radiology trainee) is defined.
7. The angiographic findings (e.g., normal artery or severe disease, etc.) are given.
8. Neurologic examination of the patient is performed by the same neurologist before and at reasonably frequent intervals, preferably for up to 72 hours, after angiography, beyond which time those patients who have experienced a change in their neurologic status should be followed for at least 1 week to determine severity.
9. All neurologic and nonneurologic events that occur during or ≤72 hours after angiography are recorded.
10. All complications are classified according to time of onset, duration (as transient [resolving within 24 hours], reversible [persisting beyond 24 hours but resolving within 1 week], or permanent), and nature (as local [e.g., hematoma, worsened claudication, ischemic foot], systemic [e.g., allergic reaction, nausea, chest pain, shortness of breath, myocardial infarction, headache, giddiness], neurologic [focal events such as TIA, disabling stroke, nondisabling stroke], or death [and cause]).
11. The frequency of complications is clearly expressed using either the number of patients or the number of procedures as the denominator.

We review eight prospective studies9,15–21 that either directly or indirectly address the complication rate of cerebral angiography for patients with mild ischemic cerebrovascular disease (Table 1) and seven
TABLE 2. Complications of Conventional Cerebral Angiography in Seven Retrospective Studies

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<th>Author</th>
<th>Mean age (yr)</th>
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<th>Transient/reversible (%)</th>
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Skalpe and Anke16 performed cerebral angiography in 100 patients in 1981 and 1982. The aim of the study was to compare the complication rates between different nonionic contrast media. The indications for cerebral angiography were not stated, only the radiologic diagnoses, which included “arteriosclerotic disease” in 42 patients. The analysis did not consider any of the diagnostic groups individually, so it is not possible to disentangle the complication rate for patients with TIA's or mild ischemic stroke. Three neurologic complications were reported, two TIA's and one minor stroke with symptoms lasting several days, and in each case the presenting history had...

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suggested a diagnosis of cerebrovascular disease. For the purposes of our review these results can be interpreted as a total neurologic complication rate of 7.1% (4.8% transient, 2.4% reversible). The authors stated in their discussion that “an important question which still remains unanswered is whether the influence on the prognosis in various cerebral lesions [e.g., ischemic cerebrovascular disease vs. other disease] may be different with non-ionic and ionic contrast media.” Unfortunately, this question was not addressed in a subsequent paper.30 The authors incidentally found no significant difference in side effects between the different contrast media.

Earnest et al17 studied 1,517 consecutive cerebral angiographic examinations in 1,387 patients during

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**Figure 1.** Statistical overview of total neurologic complication rate for cerebral angiography. Studies have been grouped as prospective studies of conventional cerebral angiography, retrospective studies of conventional cerebral angiography, and studies of intravenous digital subtraction angiography (IV-DSA). Horizontal lines are 95% confidence intervals (CIs) of complication rate for each study (the shorter the lines, the better); small vertical lines are actual observed rates.

**Figure 2.** Statistical overview of permanent neurologic complication rate for cerebral angiography. Studies have been grouped as prospective studies of conventional carotid angiography, retrospective studies of conventional cerebral angiography, and studies of intravenous digital subtraction angiography (IV-DSA). Horizontal lines are 95% confidence intervals (CIs) of complication rate for each study (the shorter the lines, the better); small vertical lines are actual observed rates.
were classified as transient if they completely resolved ≤24 hours after onset, reversible if they persisted for >24 hours but resolved within 1 week, and permanent if they had not resolved after 1 week. “Cerebrovascular disease” was the indication for 637 (42%) of the examinations. What kind(s) of patient this category actually embraced is uncertain. The patients with cerebrovascular disease were older than those with other indications for angiography.

Neurologic complications occurred in 4.2% of the examinations in patients with symptomatic cerebrovascular disease (3.4% transient, 0.2% reversible, 0.6% permanent). Among these patients, neurologic complications occurred in five (9.8%) examinations in patients with a recent stroke (four complications were transient) and in seven (10.8%) examinations of 65 patients with a history of frequent TIAs (six complications were transient). Although angiography in patients with a history of frequent TIAs or recent stroke was associated with a higher risk of reversible and permanent neurologic complications than in the remainder of patients undergoing cerebral angiography, this difference was not statistically significant. Of the patients who had a catheter exchange, four (1.4%) with cerebrovascular disease suffered reversible or permanent neurologic complications compared with only one patient (0.5%) without cerebrovascular disease. This difference was not statistically significant, perhaps owing to the small number of complications. The difficulty with interpreting some of the findings lies in the imprecise definition of “cerebrovascular disease” as the indication for cerebral angiography. Analysis and discussion were directed at patients with a history of frequent TIAs or recent stroke, but these were only a minority of those with “cerebrovascular disease.”

Ball et al18 compared complications related to IV-DSA in 500 patients with those related to conventional angiography in 150 patients, all referred for evaluation of “extracranial carotid occlusive disease” in 1982 and 1983. Selection of the angiographic procedure for each patient was nonrandom. The patients having IV-DSA were a heterogeneous group including outpatients and referrals from other centers. Radiology residents performed the cerebral angiography under supervision; the transfemoral route was used in 138 patients (92%), and the carotid arteries were selectively injected in 89%. During conventional angiography, an average of 65 (range 15–200) ml contrast (meglumine iothalamate) was administered to each patient, whereas during IV-DSA the mean volume of contrast was 148 (range 35–225) ml per patient. Observations were recorded on all patients within the Radiology Department during and immediately following angiography. It is not stated who made the observations and whether a complete neurologic examination was performed. Follow-up data were obtained the next day for all patients undergoing conventional cerebral angiography but for only the first 100 patients undergoing IV-DSA. The follow-up data were obtained from a telephone interview of the outpatients (how many is uncertain) undergoing IV-DSA and a telephone survey of the physicians and/or nurses caring for the inpatients. A standard list of questions was not used, only open-ended questions.

Ball et al18 recorded 100 complications (20% of 500) in 83 patients (17% of 500) having IV-DSA and in 11 patients (7%) having conventional cerebral angiography. With IV-DSA, the authors recorded 10 (2%) local, 75 (15%) systemic, and 15 (3%) neurologic complications. The most common systemic complications were allergic phenomena (pruritis, periorbital edema). Chest pain significant enough to terminate angiography developed in 23 patients, and eight patients had acute shortness of breath. Symptoms that Ball et al18 recorded as neurologic complications consisted of light-headedness in five (1.0%), headache in five (1.0%), syncope in two, transient loss of vision in one, seizure in one, and progression of hemiparesis to completed stroke in one patient. The vast majority of the authors’ neurologic complications were nonfocal events that may not have been considered neurologic complications in other studies or even noted in several retrospective studies. For our purposes only focal neurologic events will be classified as neurologic complications, of which there were three (0.6%), one of which was permanent. Following conventional cerebral angiography, there were six local complications (4.0%), five systemic complications (3.3%), and one neurologic complication, all of which occurred ≤18 hours after the examination. This study suggested that, except for neurologic complications related to the placement of an arterial catheter and hematoma at the site of catheter insertion, the incidence of all other complications was greater with IV-DSA than with conventional cerebral angiography for the evaluation of extracranial carotid occlusive disease. The authors concluded that one reason for the increase in complications with IV-DSA was the rapid injection of high volumes of hypertonic contrast media and the resultant hemodynamic and cardiac electrophysiological effects. Methodologic problems with this study include selection bias for the patients and angiographic procedure, lack of neurologic examination before and at serial intervals after angiography, incomplete and inconsistent follow-up, and the performance of the procedure by radiology trainees. It is also not possible to ascertain which patients were investigated for TIA and which had stroke, the
severity of the stroke, or the timing of the TIA or stroke.

Gasparini et al.18 studied 218 consecutive patients undergoing diagnostic transfemoral cerebral angiography, excluding urgent procedures. Only 86 patients had a history of “ischemia.” The mean age of all patients was 49.5 years. Diatrizoic acid contrast was used in 97% of the cases. A neurologic assessment was undertaken 24 hours before and after the procedure. No serious local or systemic complications were observed in the series, but the limits of “serious” were not defined. The neurologic complication rate for the 86 patients with TIA/stroke was 5.8% (five patients); complications were transient in two (2.3%) and reversible in three (3.5%). No permanent neurologic complications were recorded. Methods of follow-up of patients with complications were not stated. Subsequent analysis dealt with those with cerebrovascular disease alone but with the entire group of patients. This study did not specifically address patients with ischemic cerebrovascular disease and did not define “serious” nonneurologic complications. It is uncertain whether there were any local complications such as hematomas or whether such complications occurred but were not considered serious enough to report.

Jeans et al.19 studied 135 patients having cerebral angiography following the detection of neck bruits or an abnormal Doppler ultrasound study. The contrast used was initially meglumine iothalamate and later iopamidol 300 (when available). The presenting symptom was TIA in 66 (49%), amaurosis fugax in 44 (33%), and a stroke with recovery in 19 (14%) patients. Six patients (4%) had an asymptomatic carotid bruit. The aim of the study was to assess the value of an angiographic technique using three views of the carotid bifurcation, not to examine complications specifically. Nevertheless, complications were recorded which, although not defined, are worthy of inclusion in this review. An appreciable hematoma developed at the puncture site in 19 patients (14%). According to our definitions, a transient neurologic deficit occurred in five, a reversible deficit in one, and a permanent neurologic deficit in four patients. One patient died of a nonneurologic cause. This study did not set out to study complications of cerebral angiography specifically and therefore did not provide any information on the definition of complications and the timing and nature of neurologic examinations and follow-up.

Dion et al.20 evaluated clinical events following 1,002 consecutive cerebral angiography procedures in 724 patients in 1983 and 1984. In 26% of the cases, some clinical information had to be retrospectively gathered from the chart records, mostly for urgent cases in whom the preliminary neurologic examination was done by various other physicians. Otherwise, each patient had a neurologic examination by the same neurologist before, 24 hours after, and 72 hours after angiography. The transfemoral route was undertaken in all but seven patients, and ionic contrast (meglumine iothalamate) was used. A neurologic event was defined as any neurologic sign or symptom occurring during or 72 hours after angiography, whether a manifestation of the primary disease or not; the event was classified as transient if it lasted <1 week and as permanent if it lasted >1 week. A nonneurologic event was defined as any sign or symptom occurring either locally at the puncture site or systemically. Two hundred eighty-five (28%) procedures were performed to investigate “TIA/stroke.” A history of TIAs was present for 190 of the procedures and of stroke for 174. These patients were significantly older than the other patients for whom angiography was performed, more catheters and guidewires were used, and the procedure lasted longer. Between 0 and 24 hours after angiography, seven patients (2.5%) with TIA/stroke suffered a neurologic event, all of which were transient. Over the next 2 days (24–72 hours after cerebral angiography) six patients (2.1%) had a neurologic event; two events (0.7%) were permanent. This is a particularly important observation as no other prospective study has attempted to document the onset of complications during this period. Whether any or all of the events between 24 and 72 hours after angiography were actually caused by the procedure is of course uncertain.

In the study by Dion et al.20 the TIA patients showed a trend toward having more neurologic events during the first 24 hours than the remainder of the patients studied, but age, number of catheters, and duration of the procedure probably did not significantly increase the risk. The only factor that significantly increased the number of neurologic events between 24 and 72 hours after angiography was the volume of contrast material used. Local complications, almost all of which were hematomas, occurred in 14% of the patients with TIA/stroke, a rate significantly greater than that in the other patients. Most of this paper addresses the complications in the group of 1,002 angiograms as a whole, and the authors only occasionally refer to the TIA/stroke group, which itself was not defined. Uncertainty prevails over the number, timing, and clinical severity of the TIAs and strokes. The angiographic findings (i.e., degree of carotid stenosis), which may be predictive of risk/outcome, were not published.

Between 1981 and 1984, McIvor et al.21 studied 230 cerebral angiograms in 229 patients, 112 of whom had suffered one or more TIAs and 117 of whom had sustained strokes with more prolonged deficits but no serious disability. All patients were considered fit for reconstructive surgery if that was to prove appropriate. The first 98 angiograms were carried out with ionic contrast media (meglumine iothalamate and sodium iothalamate) and the following 132 with nonionic contrast medium (iohexol). A consultant radiologist performed 185 examinations, and the other 45 were partly or completely performed by one of 10 trainees. Patients in whom the examination posed a particular risk owing to recent stroke, fre-
quent TIAs, or widespread vascular disease were allocated to the experienced radiologist. Catheterization was carried out by the transfemoral route in 95% of the cases, and the carotid arteries were selectively catheterized in 97% of the examinations. A neurologic examination was performed on the patient's return to the ward, usually 1 hour after the procedure, by the junior resident responsible, and again 5 and 24 hours later. All patients for whom any neurologic deficit was reported within the first 24 hours after angiography were assessed immediately and again after 24 hours, 1 week, and 1 month by a neurologist. Immediate neurologic complications occurred following 26 (11.3%) examinations. The complications were not classified according to severity but only as “ranging from hemiplegia and blindness to minor alterations in muscle power or small visual field defects.” After 24 hours, 19 patients still had a neurologic deficit; at 1 week a deficit remained in 13 and at 1 month in 11. Therefore, according to our more conventional definitions, there were seven (3.0%) transient neurologic events, six (2.6%) reversible events, and 13 (5.7%) permanent events. The 11 patients with persistent deficits at 1 month were classified as having either major (five) or minor (six) disability. The five patients with major disability all had radiologic evidence of carotid artery disease, but there was no significant difference between the patients with or without complications when categorized according to their angiographic abnormalities. The only factor significantly associated with postangiographic neurologic morbidity was performance by a trainee radiologist. The examinations carried out by radiologists in training took on average 27% longer, most of the extra time being spent manipulating the catheter around the origins of the carotid arteries while attempting selective catheterization. It was concluded that most of the neurologic complications of cerebral angiography may have been due to catheter manipulation, probably dislodging fragments of atheromatous plaques in the proximal large arteries.

Aaron et al29 studied the complications of IV-DSA in 102 patients evaluated for carotid artery disease. The primary presenting complaints were TIA (n=38), transient monocular blindness (n=18), cervical bruit (n=12), stroke (n=27), syncope (n=4), vertigo (n=11), postoperative follow-up (n=11), and memory loss (n=2). Patients with multiple complaints were listed more than once. Only the first four groups (collective n=95) are relevant to our review, but they were not separately subcategorized. Seventy-four patients had multisystem disease (which was not actually defined), and 30 had angina. Their average age was 66 years. Patients with serum creatinine levels of >2.5 mg/dl were not examined. The IV-DSA procedures were performed by trainees with at least 6 months' experience, and diatrizoate meglumine sodium contrast was used in each case. Complications were recorded if they occurred ≤24 hours after angiography. A major event was defined as a complication with the potential to significantly alter the physical status or well-being of the patient. The term “transient” implied resolution of the problem within 10 days. Follow-up was performed either by chart review or by contacting the physician and/or patient. Serial neurologic examinations were therefore probably not performed. It was not stated over what time period follow-up ensued.

Aaron et al29 reported 55 complications involving 37 patients. Three local complications developed (two hematomas), and all were minor and transient. The authors recorded 35 systemic complications, of which 13 were minor and transient, 20 were major and transient, and two were major and permanent. The major systemic complications were cardiovascular in nature (one cardiac arrest, two myocardial infarctions, five symptomatic arrhythmias, 12 cases of chest pain, and three of major electrocardiographic changes without symptoms). The authors recorded 17 neurologic complications, of which 10 were nonfocal and classified as minor and transient (nine cases of dizziness and one headache), six were major and transient (two TIAs, two seizures, one visual disturbance, and one case of confusion) and one was major and permanent (a stroke). For our purposes, only the focal neurologic events will be interpreted as neurologic complications and the nonfocal events will be regarded as systemic; we recorded 45 systemic (44%) and seven neurologic (6.9%) complications. The authors considered those lasting up to 10 days to be transient, so some complications in this study may actually have been reversible by our criteria. No statistically significant correlation was found between the degree of carotid stenosis and the incidence of “all complications.” Of the 74 patients with multisystem disease 30 (41%) had a complication, whereas only seven (28%) of the 25 patients with carotid symptoms alone had a complication. Although these differences were not statistically significant, the authors suggested that the risk of complication may depend more on the patient's general health and presence of systemic disease, particularly in view of the lack of correlation between the degree of carotid stenosis and complications. Aaron et al29 attributed their relatively high morbidity rate to the prospective nature of the study (patients who were asked about their symptoms and carefully monitored declared significant side effects that might have otherwise not have been recorded) and the specific patient population examined (those with carotid artery disease). This study was flawed for the purposes of our review by heterogeneous patient selection (up to 28 cases were irrelevant), the apparent lack of a preangiographic neurologic examination, the fact that angiography was not performed by a consultant radiologist, the generous definition of “transient” (up to 10 days), and the follow-up over an uncertain period by only chart review or contacting the patient/physician.

Finally, a large prospective study of 5,531 cerebral angiograms performed in 3,730 patients between 1970 and 1974 was carried out by Olivecrona.31 Unfortunately, patients were not grouped according to the indication for cerebral angiography, so it is
impossible to determine the complication rate of angiography in the patients with cerebrovascular disease as opposed to those with other intracranial disorders. Also, direct carotid puncture was undertaken in 38% of the examinations, representing a considerable difference in angiographic technique from that of the studies that are reviewed as well as from current practice. This study was, therefore, not included in our review.

**Retrospective Studies**

From the Joint Study of Extracranial Occlusion (Hass et al\(^\text{22}\)) between 1961 and 1965 (Tables 2 and 3, Figures 1 and 2) emanated a large series of 4,748 patients with ischemic cerebrovascular disease who had cerebral angiography. It is not clear whether this was a prospective or a retrospective study and, if prospective, whether the patients were included before or after cerebral angiography. Irrespective, the methodology was “nonideal” in many other ways for our purposes. The angiographic protocol differed among participating institutions. Either local or general anesthesia was used. Direct carotid puncture was performed in 3,901 patients (82%), direct vertebral puncture in 58 patients (1%), and direct puncture of the aorta or ventricle was occasionally performed. Complications occurring ≤72 hours after angiography were reported. The rate of death or permanent hemiparesis was 1.2%. No differentiation was made between nonneurologic and minor neurologic complications. The local, systemic, and transient neurologic complications were grouped together, and the cumulative complication rate was 32.2%; most complications were local.

Swanson et al\(^\text{23}\) coordinated a cooperative study in six North American centers of 1,307 TIA patients, among whom cerebral angiography was performed in 464. Although it was one of the aims of the study to determine the usual diagnostic procedure for TIA patients and the complications of therapy, the authors did not specifically intend to determine the complications of cerebral angiography. Considerable variation among the participating centers existed in angiographic technique and frequency, the latter ranging from 12% to 82% of patients. Direct percutaneous carotid catheterization was performed in 21% of the cases and direct verteobasilar injection in 2%. Within 24 hours after cerebral angiography, complications occurred in 58 (12.5%) patients; all but four complications were transitory, but “transitory” was not defined. The transitory complications were local in 19 (41.1%), systemic in 10 (22.2%), and neurologic in 25 (5.4%) patients. Permanent neurologic complications occurred in three patients (0.6%), and there was one death (0.2%) in a patient who had an intracerebral hemorrhage and not TIAs. How this patient satisfied the inclusion criteria for the study is a mystery since he was deeply comatose and terminal at the time of cerebral angiography. Fauht et al\(^\text{24}\) examined the records of 147 patients who underwent cerebral angiography by femoral catheterization for evaluation of TIA or thrombotic stroke by “members of the radiology department.” The mean age of the patients was 57 years. Neurologic complications occurring ≤24 hours after angiography were documented in 18 patients (12.2%); 10 complications (6.8%) were recorded as transient (although “transient” was not defined), and eight (5.4%) were present at the time of discharge (permanent). It is assumed that the former comprised patients with both TIA and minor stroke and that the latter complications were major strokes. Of 43 patients evaluated for completed infarctions without TIAs, none had complications. Following multivariate analysis of 21 possible risk factors, those that correlated with increased risk of complications following cerebral angiography were the number of previous TIAs (p < 0.001) and the presence of arterial stenosis exceeding 90% (p < 0.03). Unfortunately, it is just these patients in whom angiography may be most indicated.

Eisenberg et al\(^\text{25}\) studied 301 TIA patients who underwent transfemoral bilateral cerebral angiography in 1974–1979. Complications were recorded if they occurred ≤24 hours after angiography and were considered transient if they persisted for <10 days. Neurologic complications occurred in four patients (1.3%), and all complications resolved within 48 hours. Reilly et al\(^\text{26}\) assessed 148 patients who had a carotid endarterectomy with preceding IV-DSA (54 patients), IA-DSA (41 patients), or conventional cerebral angiography (53 patients) and aimed to compare the results of these different techniques in the visualization of the carotid artery, not to compare complication rates. As a result, complications and physical status of the patients were not defined. The patients were not randomized; the vascular surgeon chose the vascular imaging technique. The mean age of each group was 68 years, but the groups differed with respect to symptomatology. The mean volume of contrast given also differed (144 ml for IV-DSA, 88 ml for IA-DSA, and 67 ml for conventional cerebral angiography). With IV-DSA there were seven complications; five (9%) were minor (three hematomas and two raised creatinine levels) and two (4%) were major (one dye reaction and one ventricular arrhythmia). Following IA-DSA there were eight complications; five (12%) were minor (three hematomas and two raised creatinine levels) and three (7%) were major (two TIAs and one dye reaction). After conventional angiography there were 16 complications; 14 (26%) were minor (10 hematomas and four raised creatinine levels) and two (4%) were major (one dye reaction and one vessel occlusion (which?) requiring thrombectomy). This paper examined only patients who had undergone a carotid endarterectomy. This introduces a major bias because if there were any serious complications of cerebral angiography, then the patients would not have had a carotid endarterectomy and would not, therefore, have been entered into the study.
Thomson and Thomson\(^2\) retrospectively evaluated 314 patients undergoing cerebral angiography between 1982 and 1983, of whom 213 (68%) had ischemic cerebrovascular disease. The complication rates for these patients were not specifically addressed, but it can be deduced from the article that there was only one permanent (0.5%) and no transient neurologic complications. There was no information on local or systemic complications.

Theodotou et al\(^{28}\) examined 159 cerebral angiograms from 152 patients with carotid stenosis who later had a carotid endarterectomy. The mean age of the patients was 63 years. The angiograms were categorized according to the patient’s presenting problem; 21 were for asymptomatic carotid bruit, 89 for TIA, 13 for stroke-in-evolution, and 36 for completed stroke. All studies were performed under the supervision of a trained neuroradiologist, and both carotid arteries were selectively catheterized via the femoral route. Complications were recorded if they occurred \(\leq 24\) hours after angiography. Neurologic complications related to cerebral angiography developed after five procedures (3.1%); all these patients had severe carotid stenosis. Patients with asymptomatic carotid bruit or completed stroke had no complications; those patients with TIs and stroke-in-evolution had complication rates of 4.5% (four cases) and 7.7% (one case), respectively. All complications occurred \(\leq 30\) minutes after cerebral angiography, all lasted \(<1\) hour, and there was no correlation except with the presence of bilateral severe carotid stenosis, but the numbers were very small. It was concluded that patients with stroke-in-evolution represented too high a risk to embark on cerebral angiography (and carotid endarterectomy) until stabilization occurred. This conclusion was based on a sound retrospective study, but the high complication rate of 7.7% was due to only one complication in 13 patients, and hence the confidence intervals (CIs) were very wide. Like the study of Reilly et al\(^{26}\) only patients having carotid endarterectomy were studied. Those patients who suffered a severe postangiographic stroke would not have been considered for carotid endarterectomy and would have been excluded from the study. This leads to an underestimate of the angiographic complications in this series.

Finally, Mani et al\(^32\) reviewed the complications following 5,000 cerebral angiograms performed in two training and two nontraining hospitals between 1969 and 1975. Clinical vascular occlusive disease was the indication for cerebral angiography in 1,702 patients (34%), but this group included an uncertain number of patients with primary intracerebral hemorrhage. Complications were recorded if they occurred \(\leq 24\) hours after angiography and were classified as transient if they persisted for \(\leq 10\) days. The combined systemic and neurologic complication rate for patients undergoing cerebral angiography for vascular occlusive disease was 1.6% overall (\(n=28\), 0.06% permanent) and there was no mortality, but a further breakdown of only neurologic complications was not described. It is not possible to extrapolate the neurologic complication rate of cerebral angiography for patients with ischemic cerebrovascular disease from this paper because the subset of patients with vascular occlusive disease was contaminated with cases of primary intracerebral hemorrhage and the neurologic complication rate in isolation was not available. The permanent complication rate included only those complications persisting beyond 10 days, whereas most other comparable studies applied a limit of 1 week. This paper was therefore not included in our review.

**Why Estimate the Risk of Complications From Cerebral Angiography for Patients With Mild Ischemic Cerebrovascular Disease?**

It is generally accepted that cerebral angiography is a necessary investigation before undertaking carotid endarterectomy.\(^2\) If patients with symptomatic extracranial carotid artery disease are to benefit from carotid endarterectomy, then it must be shown that the combined risks of cerebral angiography and carotid endarterectomy do not exceed those of patients treated only medically. It is therefore just as important to know the complication rate of cerebral angiography as it is to know the complication rate of carotid endarterectomy (because they are additive), but current attention seems to be mainly directed at seeking the latter. To answer this very important question, given the efforts being directed into determining the efficacy of carotid endarterectomy, only a "best guess" can be obtained by extrapolating the most pertinent information from the best available studies and attempting to interpret it accurately.

No prospective studies exist that conform to all the criteria for an ideal study outlined above and specifically address the complication rate of cerebral angiography for patients with TIA or mild ischemic stroke who are being considered for carotid endarterectomy. Retrospective studies probably underestimate the true complication rate and thus cannot be relied upon except possibly to identify prognostic variables.

It is important not to overinterpret the collective findings of these studies because they are heterogeneous in their aims (i.e., in several studies the complication rate of cerebral angiography was an incidental feature), in the types of patients studied (i.e., nonvascular cases were included in many studies), and in their definitions of complications (i.e., nonspecific events such as dizziness and headache were either not recorded in some studies or were classified as either neurologic or systemic complications).

The studies of Earnest et al\(^17\) and Dion et al\(^20\) are superior in terms of methodology and analysis but were aimed mainly at determining the complication rate of cerebral angiography for all patients undergoing this procedure (i.e., including those with cerebral aneurysm, arteriovenous malformation, and tumor) and not for patients with TIA/mild ischemic stroke specifically. These populations cannot be
assumed to be at equal risk of postangiographic complications, and the data for each need to be analyzed separately. Nevertheless, from the available information on the cerebrovascular cases in these two studies there was considerable agreement concerning the total (4.2% and 4.6%, respectively) and permanent (0.6% and 0.7%, respectively) neurologic complication rates.\textsuperscript{13,20} It is noteworthy, however, that six of the 15 neurologic complications recorded by Dion et al\textsuperscript{20} occurred 24–72 hours after cerebral angiography. Such "late" events have not been collected in other prospective studies although the events might more often be a manifestation of the underlying disease than of angiography.

\textbf{What Is the Risk?}

We review 15 studies (eight prospective and seven retrospective) from which a complication rate for conventional cerebral angiography in patients with mild ischemic cerebrovascular disease can be extrapolated. Three studies of IV-DSA (two prospective) and one study of IA-DSA (retrospective) are also reviewed.

\textit{Conventional Cerebral Angiography}

The eight prospective studies collectively comprised 2,227 patients with ischemic cerebrovascular disease.\textsuperscript{9,13,22–28} The overall combined total neurologic complication (the great majority were TIA or stroke) and mortality rate was 4.1% (95% CI 3.3–5.0%), the permanent neurologic complication rate (almost all were strokes) was 1.0% (95% CI 0.6–1.5%), and the mortality rate was 0.06% (95% CI 0–0.18%). These figures may be underestimates because they are influenced mostly by the largest study,\textsuperscript{15} in which relatively few complications were recorded; there were no permanent complications or deaths and the total neurologic complication rate was only 0.9%. The presence or absence of minor local, systemic, or neurologic complications, which were not infrequent in many of the other studies, was not mentioned.

The seven retrospective studies\textsuperscript{22–28} examined a total of 6,085 patients, and the overall combined total neurologic complication and mortality rate was 1.9% (95% CI 1.6–2.2%), the permanent neurologic complication rate was 0.6% (95% CI 0.4–0.8%), and the mortality rate was 0.6% (95% CI 0.4–0.8%). These results were heavily weighted by the large Joint Study of Extracranial Occlusion.\textsuperscript{22}

While acknowledging the influence of the largest studies in each group, it is interesting to note the (two times) greater rate of total and permanent neurologic complications in the prospective studies and the (fifteen times) greater mortality rate in the retrospective studies, almost certainly indicating a failure to record nonfatal events in the retrospective studies. The greater incidence of more minor events in prospective studies and the heavier emphasis on fatal events in retrospective studies is well recognized, as outlined earlier, and explains our greater emphasis on examining and promoting prospective studies.

It should be noted that several of the studies included any neurologic event occurring \(\leq 24\) hours after cerebral angiography as a neurologic complication. It is likely that some of these events were in fact continuing manifestations of the natural history of the underlying disorder (i.e., TIA's), which are difficult, if not impossible, to differentiate from complications of the procedure. In 1966, Baum et al\textsuperscript{33} evaluated 1,600 consecutive vascular catheterization procedures and found a striking similarity between the incidence, manner of onset, and nature of untoward reactions in cases that were cancelled \(\leq 24\) hours before the originally scheduled angiogram and those occurring \(\leq 24\) hours after angiography had been performed; of course, the patients may have had their procedures cancelled \textit{because of} continuing or recurrent symptoms, thus making any such study difficult to interpret.

Conventionally, clinical events occurring during or \(\leq 24\) hours after cerebral angiography have been considered procedure-related, and this criterion may be either conservative or liberal. After the catheter is withdrawn, the subsequent onset of a stroke may be disputed as being related to the procedure, whereas an iatrogenic focal dissection of the arterial wall may remain asymptomatic or become symptomatic weeks later when a secondary thrombus manifests itself. Future studies must continue to include all events that occur after angiography, but it needs to be recognized that to document all complications this method will probably slightly overestimate the real complication rate of cerebral angiography. On the other hand, we may underestimate the real complication rate because of publication bias, whereby only those investigators with "acceptable" complication rates publish their data.

From the published prospective study data, it would appear reasonable to suggest that the overall risk of conventional cerebral angiography in patients with mild ischemic cerebrovascular disease may be in the order of 4% for any focal neurologic complication (mainly TIA/stroke), 1% for a permanent neurologic complication (stroke), and \(<0.1\%\) for mortality. It is not reasonable, however, to extrapolate an overall local and systemic complication rate as this information was available in only very few studies and the results were quite variable.

\textit{Intravenous Digital Subtraction Angiography}

The three studies of IV-DSA\textsuperscript{18,25,29} accumulated 656 patients, with a total neurologic complication rate of 1.5% (95% CI 0.6–2.4%) and a permanent neurologic complication rate of 0.3% (95% CI 0–0.7%); no fatalities ensued. The majority of complications were systemic and mainly allergic or cardiovascular in nature. The overall systemic complication rate for IV-DSA was 18.9% (95% CI 15.9–21.9%), and the local complication rate was 2.4% (95% CI 1.3–3.6%). It would appear that the
imprecise resolution and high systemic complication rate of IV-DSA detracts from any utility in the investigation of patients with symptomatic extracranial carotid artery disease.

**Intra-arterial Digital Subtraction Angiography**

We reviewed only one study of IA-DSA26 (which was retrospective) with a neurologic complication rate of 4.9%, but the sample size was too small (n=41) to allow serious interpretation of IA-DSA itself. Further studies are needed. In the interim, IA-DSA seems to be of use in evaluating the carotid system mainly because of the smaller volume of contrast used, but it is noteworthy that in the only available comparative study27 the mean volume of contrast used with IA-DSA (88 ml) exceeded that used with conventional cerebral angiography (67 ml).

**What Causes the Complications of Cerebral Angiography?**

The causes of the varying complications of cerebral angiography are incompletely known, but several clues emanate from examination of the risk factors that have been identified in the various studies as predictive of a particularly high morbidity.

The potential risk factors for complications following cerebral angiography identified as statistically significant in any study reviewed were the patients considered (i.e., those with cerebrovascular disease as opposed to those with other neurologic disorders having cerebral angiography) for both local and neurologic complications,20 stroke-in-evolution,28 increasing number of previous TIAs,24 carotid arterial stenosis of >90%,24 bilateral severe carotid stenosis,28 greater volume of contrast administered,20 and cerebral angiography performed by inexperienced radiology trainees.21 Some of these features (such as carotid artery disease,21 TIA and stroke-in-evolution,28 and frequent TIAs and recent stroke17) also showed a trend in other studies toward predicting an increased incidence of complications from cerebral angiography while other similar trends were noted with patients of greater age,20 those in general ill health and with systemic disease,29 a greater number of catheters used and catheter exchanges,17,20 and longer duration of the procedure.20 It is noteworthy that the use of nonionic compared with ionic contrast did not appreciably affect the complication rate.21,20

Uncertainty must prevail over the results of some of these studies, which are characterized by high sampling error and very low power. Nevertheless, the potential risk factors identified are consistent with the logical conclusion that complications from cerebral angiography may be reduced if patients are carefully selected (i.e., those who are physiologically younger, systemically well, and neurologically stable) and if angiography is performed by a skilled neuroradiologist using the minimum contrast volume and catheter exchanges and in the shortest possible time. The pathologic substrates for these complications are probably numerous (regional thrombosis, thromboembolism, vascular spasm, arterial dissection, air embolism, and contrast toxicity).

Shehadi and Toniolet24 reviewed 302,083 prospective reports of intravascular contrast reactions for the Committee on Safety of Contrast Media of the International Society of Radiology. These authors determined a 4.8% incidence of reaction to intravenous contrast material. The risk from arterially injected contrast material was 2.1%. Only 12,771 of these reports (4.2%) were associated with cerebral angiography, and the adverse reaction rate in this group was 2.06% (n=263), with one case fatality. The cerebral angiography group was not subcategorized into those receiving intravenous or intra-arterial injections.

The high incidence of systemic complications associated with IV-DSA appears to be due to the rapid intravenous injection of high volumes of hypertonic contrast media. The risk of arterially injected contrast media is less, not only because of the lower dose of contrast used, but probably also because the pulmonary capillary bed is bypassed. The greater contrast load (70 g iodine) used routinely in IV-DSA than in conventional cerebral angiography (50 g) has particular implications in patients with borderline cardiac or renal reserve.35

Nephrotoxicity was not specifically addressed in the studies reviewed, but a prospective study of changes in renal function over 72 hours after nonrenal angiography in 315 patients (131 aortoiliacofemoral, 97 carotid-vertebral, 87 splanchic) has been reported.36 In the 97 patients having carotid-vertebral angiography, serum creatinine concentration rose by 0.5–0.9 mg/dl (50–90 μmol/l) in three patients and by >1.0 mg/dl (100 μmol/l) (indicating acute renal failure) in one patient. The nephrogram was borderline in three and positive in four patients. Analysis of all the patients revealed that the single risk factor significant for developing acute renal failure was the presence of preexistent azotemia (blood urea nitrogen concentration of 30 mg/dl [10 mmol/l] and serum creatinine concentration of 1.5 mg/dl [150 μmol/l]). The authors recommended a screening serum creatinine determination 24–48 hours after infusion of angiographic contrast material in azotemic patients.36 This has particular relevance to IV-DSA.

**Are These Complication Rates Generalizable to Other Institutions?**

The risk of cerebral angiography naturally varies from one medical institution to another, in much the same way as it does for carotid endarterectomy, mainly because of differences in patient selection and radiologic facilities and expertise.17 The collective results from our review cannot really be generalizable to all medical centers but can be used only as an approximate guide. All medical institutions performing cerebral angiography for ischemic cerebrovascular disease need to monitor their own results and complications of cerebral angiography, in much the
same manner as for carotid endarterectomy, by means of a formal ongoing audit performed preferably with the assistance of one or more disinterested parties. Only then will the truly relevant complication rate, the rate in one’s own institution, be known.

What Are the Implications of the Risk of Cerebral Angiography?

Estimating the risk of cerebral angiography for patients with mild ischemic cerebrovascular disease is an important priority, not only because of the potential increase in cerebral angiography should carotid endarterectomy be shown to have a definite role in the management of these patients, but also because of its already widespread use. The number of patients having cerebral angiography for ischemic cerebrovascular disease must be several times greater than the number who proceed to carotid endarterectomy, and those who do not have carotid endarterectomy do not benefit from having “unnecessary” cerebral angiography; they stand to lose. Data from the UK-TIA Aspirin Trial indicated that of 304 patients undergoing cerebral angiography for TIAs or mild ischemic stroke, only 22% proceeded to carotid endarterectomy. From this information it can be extrapolated that, to generate 100 patients suitable for carotid endarterectomy, approximately 450 cerebral angiograms need to be performed (22% of 454 = 100). If the neurologic complication rate of cerebral angiography is approximately 4%, as we estimate, then 18 patients (4% of 450) may suffer a neurologic complication, of which four may be permanent (i.e., a major stroke; 1% of 450). Under these circumstances, up to 4% should be added to the risk of permanent stroke after carotid endarterectomy when considering whether to recommend it. So, not only does the risk of cerebral angiography need to be known and reduced, but greater scrutiny is also required in recognizing and selecting patients who may be suitable for cerebral angiography (and likely candidates for carotid endarterectomy) so as to avoid unnecessary cerebral angiography. Patients who are suspected on clinical grounds of having symptomatic extracranial carotid artery disease should initially have a duplex ultrasound (Doppler combined with B-mode imaging) examination of the neck vessels to screen out those with absent or minimal carotid disease for whom cerebral angiography may otherwise be performed “unnecessarily.” If this is done, then only the surgical candidates with moderate or severe carotid artery disease will undergo cerebral angiography, and the risks (and indeed costs) of performing angiography in patients with mild or absent carotid disease will be avoided. As a result, the absolute number of complications will be reduced. However, it must be recognized that the patients with significant carotid disease are also perhaps those more likely to suffer complications of cerebral angiography. Therefore, carotid ultrasound screening

**Figure 3.** Example of possible protocol for prospective accumulation of data on each case undergoing cerebral angiography.
may eliminate the patients at low risk for complications of cerebral angiography, leaving only those with significant carotid disease and a significant risk of complications. As a result, the risk of permanent stroke after cerebral angiography may, in fact, exceed 1%. That is, the relative risk of cerebral angiography may increase due to a reduction in the denominator (number of angiograms) while the absolute number of complications (the numerator) should fall.

What Needs To Be Done Now and How?

If carotid endarterectomy is shown to be effective in the management of certain patients with ischemic cerebrovascular disease, then optimal imaging of the carotid circulation with the lowest possible risk will be required in a very large number of patients.

Conventional cerebral angiography is the most accurate and widely used modality at present, but IA-DSA is gaining wider acceptance. There are potential advantages of IA-DSA over conventional cerebral angiography; they include a shorter procedure time and the use of lower volumes of contrast and smaller catheters. This may lead to lower complication rates, but these postulates will be answered best by a prospective randomized trial comparing IA-DSA with conventional cerebral angiography. Before proceeding to cerebral angiography, however, patients who are considered potential surgical candidates on clinical grounds should be screened noninvasively with carotid ultrasound which, although operator-dependent, should define those patients with minimal carotid disease who do not require cerebral angiography.

If surgeons are prepared to undertake carotid endarterectomy, then they should collaborate with their fellow neuroradiologists and neurologists to audit prospectively the results of their preferred angiographic technique in their own medical center, much as they should be doing for carotid endarterectomy. (The Asymptomatic Carotid Atherosclerosis Study is a randomized multicenter study of carotid endarterectomy that is currently in progress and accumulating such information in this manner.9) The audit should be feasible within the local institution, and this demands that data be collected on a protocol form that is simple, standardized, and practical, yet comprehensive enough to gather the information required to answer the initial question(s) efficiently. The ideal criteria outlined above are some guidelines for such a study, and an example protocol form has been prepared for consideration and potential modification and use (Figure 3).

In view of increasing interest in the emergency treatment of acute stroke with fibrinolytic agents, future studies will also need to consider patients with acute minor and major stroke who are to undergo immediate cerebral angiography upon admission to a hospital.

Conclusions

The management of patients with mild ischemic cerebrovascular disease can be optimized by careful clinical evaluation and sensible selection of patients for further investigation. Initial investigations should be noninvasive and include carotid ultrasonography. Only if these results are positive or equivocal should cerebral angiography be considered. If clinical assessment and carotid ultrasonography are omitted, then unnecessary cerebral angiography will result. Preoperative screening should reduce the excessive number and cost of unnecessary normal cerebral angiograms. Otherwise, the number of patients damaged by angiography may approach the number damaged by carotid endarterectomy, and taken together, this may obviate whatever advantage there may be in performing carotid endarterectomy at all.

For patients with mild ischemic cerebrovascular disease undergoing cerebral angiography, the risks of suffering a neurologic complication (TIA or stroke) are about 4%, and the deficit may be permanent in 1%. The mortality rate is <0.1%. These figures are obtained from the eight prospective studies that addressed this issue, either directly or indirectly, with varying aims and methodology. The figures are not definitive and are not generalizable to all institutions and therefore are best used as an approximate guideline. All centers performing cerebral angiography need to audit their own results, conforming as closely as possible to the ideal criteria outlined above, to obtain the complication rates that are applicable to their own practice. In the interim, it appears that the complication rate of cerebral angiography may be reduced if referring clinicians carefully select patients for cerebral angiography (physiologically younger patients who are systemically well, are not azotemic, are neurologically stable, and are highly likely to proceed to carotid endarterectomy if angiography shows an operable and relevant lesion) and if arch and/or selective cerebral angiography is performed by an active, experienced neuroradiologist using a transfemoral approach, small catheters, and a minimum volume of nonionic contrast medium, with as few catheter exchanges as possible, in the shortest possible time. Frequent neurologic examinations of the patient after cerebral angiography will identify almost all complications and may allow permanent sequelae to be prevented. Azotemic patients should have their serum creatinine concentration estimated 24–48 hours after cerebral angiography.

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