OVER THE PAST SEVEN decades, a relationship between thrombo-embolic stroke and arteriosclerotic changes of the carotid and vertebral arteries has been established. \(^1\) The role of extracranial arteriosclerotic disease in the etiology of stroke is agreed to be important, its exact contribution remains undefined. Largely responsible for this uncertainty are: the frequent co-existence of similar arteriosclerotic changes in both the cervical and intracranial vasculature; the presence of morphologically identical forms of atherosclerotic disease in comparable locations in both symptomatic and asymptomatic patients; the fact that clinical manifestations of thrombo-embolic stroke are, for the most part, related more to physiological changes than to disturbed anatomy; and heretofore the need to use invasive procedures, carrying unacceptable risks, to document the lesions of arteriosclerosis. \(^11\) \(^12\)

Once it has occurred, the course of an ischemic stroke remains to an unacceptable degree refractory to therapy, leading either to persistent neurological dysfunction or death in a majority of patients. A favorable therapeutic approach therefore must be prophylactic, a restriction requiring recognition of the population at risk before they have suffered a stroke.

Most commonly, ischemia or infarction of the brain does not represent a disease per se but rather is a nonspecific incidental manifestation of steadily progressive arteriosclerosis affecting arteries throughout the body. \(^13\) In this regard, a cohort from the general population who are at increased risk for the occurrence of an ischemic cerebrovascular accident can be identified. Hypertension, diabetes mellitus, cardiac dysfunction as measured by either clinical, radiographic or electrical parameters, smoking, obesity and stress all have been implicated as factors which serve as markers for this population. Through the use of statistical methods, a stroke risk profile can be developed based on these factors. Such a profile allows recognition of that segment of the still asymptomatic group in which half of the thrombo-embolic strokes will occur. Persons in this population have a 40 to 47% chance of suffering such a calamity within eight years. \(^12\) Others at risk may be recognized because of historical accounts of intermittent transient ischemic attacks or as a result of findings on physical examination such as carotid bruits or ophthalmoscopic abnormalities. \(^10\) \(^14\) \(^15\) \(^16\)

Over the last decade, simultaneously with the accumulation of epidemiological data, extensive efforts have been directed towards development of safe techniques for assessment of the extracranial vasculature. In this issue, articles by Gee on oculopneumoplethysmography (OPG-Gee) and by Little and his associates on digital subtraction angiography, (DSA) report recent results with two quite different approaches to this problem. The purpose of this editorial is to briefly review the capabilities and limitations of currently available methods for evaluating the vasculature incriminated in the genesis of thrombo-embolic stroke, and to summarize our opinion of a logical method for employment of these modalities.

**Digital Subtraction Arteriography (DSA)**

As a result of efforts begun in 1971, a digital image processor capable of allowing visualization of small amounts of intravenously injected iodinated contrast medium was developed and tested by Misretta and his colleagues at the University of Wisconsin. \(^17\) During this same period, digital video image programs were independently implemented at the University of Arizona. \(^18\) By February 1980, we had examined the extracranial vasculature of 100 patients with intravenous DSA. \(^19\) It is estimated today that in the USA alone there are some 200 digital subtraction angiography units in operation and 13 manufacturers currently offer commercial equipment capable of performing this type of examination. \(^20\)

Compared with conventional methods of arteriography, digital subtraction techniques offer improved contrast recognition at the expense of decreased spatial resolution (1.5–2.0 line pairs/mm compared with 6–10 line pairs/mm). \(^21\) This is an acceptable exchange because in many instances the exquisite detail possible with standard arteriography is not necessary for one to make correct diagnostic and therapeutic decisions.

Unlike traditional methods of arteriography there is no risk of neurologic damage as a direct result of an intravenous digital subtraction examination. Risks of intravenous DSA include idiosyncratic reactions to the iodinated contrast medium, possible damage to the venous system related to the injection of the contrast medium, and renal injury occurring as a result of contrast medium toxicity.

Some type of adverse reaction occurs in just under five percent of all patients who receive iodinated contrast media. Most are mild and consist of either flushing, nausea, vomiting, or mild urticaria and require no treatment. Respiratory or cardiac arrest has been en-
countered in 0.017% of patients and a 0.001% – 0.006% incidence of fatal reactions is reported. Extravasation of contrast medium into the tissues of the arm or mediastinum has occurred five times in our DSA practice and, except for pain requiring treatment, did not result in any adverse effects. All of these complications occurred before adoption of the use of a multi-hole pigtail catheter positioned in the superior vena cava. Using a peripheral arm vein injection, venous extravasations have been reported to occur at a rate of less than 1 per 1000 examinations. Candidates for intravenous DSA should be carefully screened so that those with conditions such as diabetes mellitus, multiple myeloma, or pulmonary venous hypertension may be identified prior to receiving large doses of intravenous contrast medium.

Although limited, early studies comparing the results of intravenous DSA with those obtained by standard selective common carotid arteriography have shown this technique to be accurate in demonstrating stenosis or occlusion of the extracranial cervical vasculature in the subset of those digital examinations considered technically satisfactory. Chilcoate and his associates studied 100 patients with both modalities and found that 60% of the intravenous digital subtraction examinations provided accurate visualization of both carotid bifurcations; 23% provided adequate images of one bifurcation and in 17% the examinations were not diagnostic. The intracranial vasculature was not evaluated in this study. In this issue, workers from this same group describe improved results so that now adequate visualization of both carotid bifurcations is achieved in over 85% of the patients examined with intravenous DSA and in 96% of those examined specifically because of suspected brain ischemia.

Preliminary results from an ongoing study in our department comparing intravenous DSA with standard arteriography indicate that between 10 and 15 percent of the examinations are nondiagnostic; 30 to 50 percent of the studies provide excellent visualization of both carotid bifurcations as well as of the intracranial portions of the internal carotid arteries and the proximal middle and anterior cerebral arteries; and the remainder of the examinations show only either one carotid bifurcation adequately or inadequate visualization of the intracranial vasculature. In a group of nearly 100 patients who have had both an intravenous DSA and a standard arteriogram, we have not encountered a false positive DSA examination. Two false negative DSA studies have been seen, both in patients with thin vascular webs.

The accuracy of intravenous DSA in evaluation of ulcerative disease of the extracranial vasculature has not been established. If one assumes, however, that significant ulcers are those of at least 0.5 cm in size, then it is reasonable to expect that in examinations of adequate quality, the rate of detection of these lesions will approach that of standard arteriography. Studies have not been reported comparing the results of intravenous DSA and standard arteriography in evaluation of the aortic arch.

Recently, larger pixel arrays and the integration of multiple TV images have improved the quality of digital subtraction images. No relevant data comparing these higher quality intravenous digital subtraction examinations with other methods of noninvasive testing are available. Such studies are currently under way at our institution as well as elsewhere. The usual time required for an intravenous digital subtraction arteriographic examination of the extracranial vasculature is about 45 minutes. These studies are readily performed on outpatients. In our department the total cost of an intravenous digital subtraction arteriogram is $385.

**Noninvasive Testing**

During the last decade, along with programs for the development and testing of digital video imaging devices, extensive efforts have also been directed toward the development and validation of a group of noninvasive methods for assessing the status of the cervical vasculature. The major objective of this has been to gauge either directly or indirectly the state of the circulation through the carotid arteries. Because of these endeavors, several noninvasive tests are widely available and have been shown in clinical practice to be highly accurate in the detection of hemodynamically significant lesions of the carotid circulation. Recent reviews of the capabilities and limitations of these techniques are available. Currently in common use are carotid phonoangiography (CPA), some form of direct ultrasound imaging of the carotid bifurcation (either Doppler ultrasonic imaging or B-mode ultrasonic imaging), oculoplethysmography (OPG-K), oculopneumoplethysmography (OPG-Gee), and peribital directional Doppler ultrasonography (PDDU). Other more sophisticated methods undergoing clinical testing but not yet widely disseminated are techniques which employ spectral analysis of the audio signal of carotid phonoangiograms or Doppler frequency wave form data, and instruments which combine high resolution B-mode scanning capabilities with Doppler devices (Duplex scanners).

Computer analysis of the audio signal obtained by carotid phonoangiography allows detection and quantification of the majority of those carotid bifurcation stenoses which result in a bruit. Obviously, all lesions not causing a bruit (i.e., mild stenosis, very severe stenosis, occlusions and ulcerations) will go undetected, and thus, a negative study does not exclude a significant abnormality. Significant numbers of false positive and false negative results are obtained when this technique is used in isolation. Characterization of the degree of stenosis of lesions which cause bruits correlates very well with results obtained by standard arteriography. One advantage stated for carotid phonoangiographic analysis is that it provides a rapid, simple, and safe method to obtain an objective record which can then be used to compare changes occurring over time.

The carotid bifurcation may also be examined directly using a variety of Doppler devices. Parameters related to blood flow are recorded and analyzed in either a qualitative or quantitative fashion. Through the use of these techniques, hemodynamically signifi-
Bilateral disease is more difficult to detect.30,52 Both of these methods theoretically allow recognition and characterization of multiple lesions in the same artery can not be recognized.38-40 While the devices theoretically allow recognition and characterization of the site of an obstruction is not possible and it appears that of all noninvasive testing methods this is the most dependent upon operator experience and skill.29,39,45

Other methods of indirect assessment of the carotid circulation based upon the detection of alterations of pressure within the carotid circulation have been developed. OPG-Gee measures the arterial systolic pressure within the ophthalmic arteries.46,47 Excellent correlation of these results, and those measured directly, have been reported. This technique provides an accurate method for detection of unilateral hemodynamically significant carotid lesions.48-50 Instrument modifications and techniques described in this issue indicate an increased sensitivity in detection of bilateral disease.50 OPG-K also allows assessment of pressure alterations within the carotid circulation but through detection of differences in arrival time of ocular pulses.51 Experience with this method is extensive and it has been shown to be highly accurate in detection of unilateral hemodynamically significant stenosis or occlusions. Bilateral disease is more difficult to detect.30,52 Both of these techniques (OPG-K and OPG-Gee) require topical anesthesia of the cornea. This is well tolerated by the great majority of patients.

In spite of a considerable experience with these tests, the lack of standardized techniques, the use of various combinations of the noninvasive methods, and differences in classification of the types of atherosclerotic lesions, make it impossible to define exactly either their accuracy or precision for identification of atherosclerotic changes in the cervical vasculature. Results from an appropriate combination of these tests are superior to those of any single method of examination.53, 54 When employed by skilled and experienced operators, these tests allow recognition of hemodynamically significant lesions (lumen area reduction of at least 80%) in the cervical portion of the carotid arteries about 95% of the time. They are not as accurate in detection of less severe stenosis, but still are capable of providing reasonable diagnostic information. Using these methods, it is impossible to exclude the presence of multiple lesions to localize lesions precisely, or to accurately assess the vertebrobasilar system. Ulcerative disease has not been adequately demonstrated.

A battery of 4 to 6 of these examinations can be carried out easily in 45 to 60 minutes on an outpatient basis. In our department the total charge for a noninvasive examination of the carotid arteries is $185.

**Discussion**

In the preceding paragraphs we have emphasized the well established relationship between arteriosclerosis and thromboembolic stroke. We have also given our assessment of the capabilities and limitations of both intravenous DSA and non-invasive testing in demonstrating the vascular incriminated as important in the etiology of this condition. The question remains how, then, are these modalities best employed.

A satisfactory intravenous digital subtraction arteriogram provides more information about the vasculature important in the genesis of thromboembolic stroke than does any combination of methods of noninvasive testing. This is because with the digital subtraction technique, arteries from the aortic arch to the major trunks of the cerebral vessels are visualized such that both significant ulcerative disease and all degrees of stenoses can be identified.19, 25, 55, 56 In our opinion, an additional important advantage is that the results are recorded in such form that they may be easily reviewed by those not directly involved with the test. This is not true for most of the noninvasive methods.

Noninvasive techniques have little if any place in the evaluation of patients with typical carotid artery TIA's. The role of an intravenous DSA examination in this group of patients hinges upon its ability to provide images such that operative lesions of the carotid bifurcation are demonstrated and there is satisfactory visualization of the major intracranial vasculature, thereby eliminating the need for standard arteriography. In this group of patients, only when an intravenous DSA replaces the conventional arteriogram will there be a significant savings in cost or risk.37 To date, there are no data documenting how often this may be achieved. We believe that the intravenous DSA examination holds great promise for replacing standard arteriography as a method of diagnosis for these patients. It is established that minor degrees of intimal ulceration escape detection on selective arteriograms of the best quality, and indeed may even go undetected on inspec-
tion of the vessel itself.58, 60, 69 Certainly, it will not be possible to recognize lesions such as these with intravenous DSA. Similar reasoning applies to the evaluation of those patients who have either suffered a completed stroke and have had good neurological recovery or who have signs or symptoms of retinal embolization.32, 33, 61

The patient with an asymptomatic bruit detected by physical examination has an increased risk for stroke. However, the risk is not restricted to the arterial territory from which the bruit originates.62, 63 Data also have been presented which indicates that bruits originating from hemodynamically significant lesions are more significant in this regard than are those which occur because of less severe disease.64, 65 How should one evaluate such patients? Because of the reasons previously discussed, the DSA examination of satisfactory quality will provide information superior to that achievable with noninvasive methods. However, because there are large numbers of patients with asymptomatic bruits which originate from changes not now considered as operative lesions, it seems prudent to screen these patients with noninvasive methods prior to subjecting them to any risk at all. Then, patients with hemodynamically significant stenoses may be further evaluated in the same way as are those patients with carotid artery TIA’s. We believe that similar reasoning should apply to evaluation of those asymptomatic patients who may be at increased risk for stroke because of an anticipated major surgical procedure employing controlled hypotension or nonpulsatile circulatory assist.

Many patients seek medical attention because of vague or nonspecific symptoms which are possibly related to ischemia of the brain. When the extracranial vasculature of such patients is examined a variety of abnormalities will be detected. It is obvious that in most of these there does not exist any direct relationship between the symptoms and the demonstrated abnormalities. It seems clear that not all of these patients should have either an intravenous DSA or noninvasive testing. It is unclear, however, either how to select those whom should be studied further or how to treat those in whom various morphological abnormalities are demonstrated. The use of intravenous digital subtraction arteriography in carefully controlled clinical studies has potential for clarifying the role of vascular disease in the complaints of these patients. Information obtained through the use of non-invasive testing may also be useful, however, it suffers an intrinsic deficiency because of the inability of these methods to evaluate the verteobasilar system.

Conclusions

Surgery is indicated for many of those symptomatic patients who have an operative lesion at the carotid bifurcation ipsilateral to either a cerebral hemisphere or eye which has experienced ischemia.61, 66, 67 However, controversy continues with regard to appropriate treatment for morphological changes in the extracranial vasculature of asymptomatic patients or those with nonspecific symptoms.58, 68, 69 The role of vascular anatomy in the prognosis of these patients remains undefined.

As a result of recent technological advances, we are now able to evaluate the extracranial vasculature with greater precision, accuracy and less risk than ever before. Application of the multiple modalities in carefully controlled clinical studies is required to clarify these issues. Such studies should be designed to define the natural history of extracranial atherosclerotic disease; to assess the effects of various forms of treatment, as well as to evaluate the accuracy, cost, and benefits, derived from testing with the various modalities. Protocols comparing results from various diagnostic modalities should be designed to assess not only the physical parameters of the testing devices (i.e. image quality etc.) but, to be of real significance, must also evaluate the impact of the various methods on diagnosis and patient outcome.70

Unrestrained enthusiasm for the application of either noninvasive testing or DSA is unwarranted. Until the significance of arteriosclerotic changes in the extracranial vasculature are more clearly defined, their presence should not be equated with the need for treatment. If one recognizes that these alterations are only one manifestation of a systemic vasculopathy, then the futility of applying all diagnostic and therapeutic efforts toward the carotid bifurcation alone will be readily apparent. Careful and continued investigation, coupled with caution and constraint, should be the current course.

Charles M. Strother, M.D., Andrew B. Crummy, M.D. Department of Radiology University of Wisconsin Clinical Science Center 600 Highland Avenue Madison, Wisconsin 53792

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