Noninvasive Evaluation of Arteriosclerosis
Comparison of Methods
D. Eugene Strandness, Jr.

The need for objectively identifying arteriosclerotic lesions and estimating their functional significance is obvious. From a practical standpoint, the technology required to obtain this information differs with each region of the arterial circulation. In clinical practice, both anatomic and physiologic data are helpful whenever available to provide a more complete picture of the impact of arteriosclerosis on the patient. For research purposes, the same information is desirable, but there is an added requirement. Any technique proposed for long-term studies must be sensitive enough to permit documentation of a change in the status of the disease wherever it may be located.

This paper reviews the progress made to date in diagnosing disease in two major arterial beds. The first is the extracranial arterial circulation, which is frequently involved by arteriosclerosis and may be the cause of either transient or permanent neurological deficits. The second area is the peripheral arterial circulation, which in clinical practice consists of those arteries supplying the arms and the legs. Each area will be considered separately since the clinical manifestations are obviously different, as is the technology required to evaluate the extent of disease involvement.

Traditional Diagnostic Methods

The diagnostic approaches used in clinical practice are only implemented when the patient presents either with symptoms or shows some abnormality on physical examination. Usually the next step is the performance of arteriography to delineate the location and extent of the arterial involvement. It is largely on the basis of this evaluation that most current therapy is planned. Unfortunately, physicians are forced to infer from these anatomic studies the physiologic implications of the observed lesions. Since the mechanisms involved in the pathophysiology of ischemic events tend to be different for the two major arterial beds, it is important to consider them separately to set the stage for a review of the noninvasive testing procedures currently available.

Extracranial Arterial Circulation

Patients with suspected extracranial arterial disease referred for noninvasive studies can be subdivided into three major groups: 1) those who have bruits in the neck but are free of symptoms; 2) those who have had transient ischemic attacks and completed strokes; and 3) patients with nonspecific symptoms that are possibly secondary to a reduction in cerebral blood flow due to either high-grade stenoses or total occlusion of the internal carotid artery. Our own data show that for every 100 patients coming to our laboratory, the percentage in each category is as follows: 20% will have a neck bruit but be free of symptoms; 50% will have focal, transient, or permanent neurological deficits; the remaining 30% will be in the nonspecific category.

Current clinical practice dictates that most patients with the focal symptoms should undergo arteriography regardless of the results of any other tests. However, the management of the remaining patients is less well defined, since there are no hard data yet available to indicate what the appropriate diagnostic workup and management should be.

A difficult group of patients for both noninvasive and invasive testing are those suspected of having symptoms secondary to vertebrobasilar disease. As will be noted, it is difficult to obtain information about the hemodynamics of the vertebral artery except in cases with subclavian artery occlusion where there is flow reversal in the ipsilateral vertebral artery.

At the present time, arteriography is not performed on every patient suspected of having carotid or vertebral artery disease because of the discomfort and potential risks of the procedure. Digital subtraction arteriography, however, is less uncomfortable and dangerous, since the contrast material is given via a central venous line. Thus, it is to be expected that

From the Department of Surgery, University of Washington School of Medicine, Seattle, Washington.
Address for reprints: Dr. Donald E. Strandness, Jr., Department of Surgery, University of Washington School of Medicine, Seattle, Washington 98195.
Received October 29, 1982; revision accepted January 11, 1983.
ARTERIOSCLEROSIS VOL 3, NO 2, MARCH/APRIL 1983

this new method will be used more widely in clinical practice, but a word of caution is in order. The quality of these images is often not as good as those obtained by selective arterial injections, and about 20% are totally unsatisfactory because of motion artifact.

The need for noninvasive testing as the initial diagnostic procedure in this area of the circulation is controversial, particularly for patients with transient ischemic attacks. It is the view of this author that testing can be justified if the following criteria are satisfied: 1) the test is sufficiently sensitive to detect disease at the carotid bulb for all degrees of involvement; 2) it will provide accurate information about those patients who would not be considered candidates for carotid endarterectomy, i.e., those who are normal or have total occlusions of the internal carotid artery; 3) it is useful for documenting disease progression during follow-up; and 4) it is cost-effective.

Peripheral Arterial Circulation

The clinical presentation of peripheral arterial circulation disease can be divided into symptoms with exercise and those at rest. Exercise symptoms are expressed as intermittent claudication, presenting with all degrees of severity ranging from minimal disability to an ability to walk only a few steps. Symptoms at rest represent the end-stage manifestations of arteriosclerosis, presenting as pain at rest or gangrene. For those patients who clearly fit into these two categories, the therapeutic decisions are now fairly well standardized. Direct arterial surgery is reserved for those patients with either disabling claudication or threatened limb loss. A conservative course is usually recommended for those patients with minimal to moderate claudication. The rate of limb loss is approximately 1% a year for the nondiabetic but increases to about 5% a year when the patient has diabetes mellitus.3,4

Before arterial surgery is contemplated, the arteriogram is the required test; but this is not only for diagnostic purposes. The contrast study is done to localize the involved segment(s) and, in essence, provides a road map for the surgeon. It serves this purpose well but does have serious limitations that have become more evident with the passage of time.5

Since symptoms in the lower limbs are usually secondary to a reduction in arterial flow, it is important to be able to assess the hemodynamic effects of those lesions that are of questionable significance. In the case of total arterial occlusion, one can usually be certain of the hemodynamic consequences, and arteriography permits this recognition with nearly 100% certainty. However, in cases with only arterial narrowing, it is frequently difficult to predict from the arteriographic image alone the extent to which the disease interferes with the blood flow across that segment. This interference in blood flow is most clearly evident with stenoses involving the aortoiliac segment.6 For example, when interventional radiologists contemplate a transluminal angioplasty in this area, they will perform intraarterial pressure measurements across suspicious areas to be certain that the visible lesions do indeed reduce pressure and flow either at rest or following the injection of a vasodilating agent such as papaverine.7

The noninvasive tests currently in use can provide answers to questions not available by either the clinical evaluation or the arteriographic appearance of the lesions. These tests may be applied for the following reasons: 1) diagnosis, particularly for those patients with atypical leg pain8 who are often grouped together as having "pseudoclaudication syndrome" (diseases that may produce symptoms mimicking claudication, such as spinal canal stenosis, herniated nucleus pulposus, degenerative joint disease, and in rare instances spinal cord tumors); 2) estimation of disability;9 3) location of involved segments;10 4) assessment of the status of the "runoff" arteries, vessels critical to the success of direct arterial surgery;11 5) determination of long-term follow-up;12,13 6) prediction of amputation level;14 and 7) evaluation of impotence.15

Diagnostic Methods Used in Evaluating the Extracranial Arterial Circulation

Surprisingly, recognition of the importance of the cervical carotid arteries, and in particular the carotid bifurcation, in the etiology of cerebral ischemia has been relatively recent. A great deal of credit for establishing the relationship between disease of the internal carotid and brain ischemia is due to C. M. Fisher, who reported this in 1951.16 While this was not a new observation, he focused attention on the causal relationship between extracranial carotid artery disease and cerebral infarction.

Although the importance of carotid artery arteriosclerosis is now well accepted, the mechanisms involved in the production of ischemia are often difficult to establish with certainty.17 Most investigators support the embolic theory as the most common cause, since ulceration of the plaque at the bifurcation is commonly found in patients with transient ischemic attacks and strokes (Figure 1). The emboli that originate from those areas vary from platelet clumps to cholesterol crystals. These have been most commonly seen in the retinal arteries of patients who present with amaurosis fugax.

On the other hand, there is no doubt that cerebral ischemia can also occur in patients with internal carotid artery occlusions or high-grade stenoses (Figure 2). Under these circumstances, the mechanisms involved are thought to be a sudden reduction in hemispheric blood flow and inadequate collateral blood flow via the circle of Willis.

The important association between carotid disease, transient ischemic attacks, and stroke was highlighted in a report by Thiele et al.,18 who examined the arteriograms in 109 consecutive patients presenting with either transient ischemic attacks or strokes. In the 66 patients with transient ischemic
attacks (hemispheric and ocular), only 9% had no lesion. In the 29 patients with fixed neurologic deficits, 10% had no demonstrable lesion. The remainder of the patients in both groups had disease of the carotid bulb. Plaque irregularity, used as the arteriographic sign of loss of endothelial continuity (ulceration), was noted in 84% of the patients in the study.

These considerations are of great importance in reviewing the current application of noninvasive testing. As will be discussed, many tests will be positive for only high grade lesions, while some of the newer ultrasonic imaging methods may be used to detect plaques in all stages of development. In addition, none of the available noninvasive tests will detect disease either in the carotid siphon or the intracranial branches of the carotid or vertebral arteries.

**Noninvasive Testing — Extracranial**

**Indirect Testing Methods**

The tests in this category were designed to detect disease in the carotid bulb by studying the pressure or flow changes at the level of the ophthalmic artery. Thus, by definition, these tests would be capable of detecting carotid bifurcation disease only if it were severe enough to alter the normal pressure-flow relationships across the carotid bifurcation, which in turn are reflected in those arteries that are branches of this main-stem artery.

**Periorbital Doppler Examination.** This test, popularized by Brockenbrough, Muller and Barnes and Wilson, takes advantage of the fact that the blood supply to the supraorbital region of the face is via the ophthalmic artery, which anastomoses with the medial, frontal, and supraorbital arteries. The ophthalmic artery is the first branch of the internal carotid artery inside the skull. The direction of blood flow in this artery is normally from inside to outside the orbit. The anastomoses of the ophthalmic artery with the branches in the supraorbital region also communicate with the superficial temporal artery, which is a branch of the external carotid artery. Thus, if the internal carotid artery is highly narrowed or totally occluded, the external carotid via the arteries communicating with the ophthalmic may become an important collateral supply for the ipsilateral hemisphere. This would result in a reversal of blood flow in the supraorbital and medial frontal arteries.
All that is required to assess the blood flow in these arteries is a directional continuous-wave Doppler system. The test is performed by noting the direction of flow in the medial, frontal, and supraorbital branches near the rim of the orbit and noting the effect of compression of the superficial temporal and facial arteries. If flow is in a reverse direction and if it diminishes or stops with compression of the feeding branches, the test is positive. To further evaluate other potential sources of collateral flow, Barnes et al.\textsuperscript{22} have proposed compression of the ipsilateral and contralateral common carotid arteries low in the neck.

As might be expected, this test is positive only in patients with carotid artery lesions that produce a reduction in pressure and flow to the ipsilateral hemisphere. Using all the compression maneuvers, Barnes et al.\textsuperscript{22} reported a 95% accuracy in detecting high grade stenoses (greater than 50% diameter reduction) and total occlusions (36 sides evaluated). On the other hand, the test was negative in 51 normal carotid arteries and in 59 of 63 patients with plaques that narrowed the carotid artery by less than 50%. Thus, this simple test will be useful in detecting only moderate and severe carotid lesions. A major difficulty with this test is the fact that it cannot be used to distinguish between a high grade stenosis and a total occlusion. In addition, once positive, it remains so and is of little value in documenting further progression of disease.

Oculoplethysmography. Since changes in the ophthalmic artery pressure and flow may also reflect disease in the carotid bulb and internal carotid artery, it was natural that plethysmographic techniques were developed to test the orbital circulation. At the present time, there are two basic techniques in use, which depend upon the measurement of two different variables: pulse delay and intraocular pressure.

The pulse delay method developed by McRae and Kartchner\textsuperscript{23} uses cups applied to the cornea that are subjected to a negative pressure of 50 mm Hg via connecting tubing. With the cups in place, it is possible to record ocular pulse waveforms from both globes simultaneously and compare the timing of the arrival of these pulses. The test depends entirely upon detecting a difference between the two eyes. Photoelectric sensors are also applied to both earlobes to monitor the pulse arrival times between the external carotid arteries and was designed to be helpful in detecting disease of the external carotid and/or bilateral lesions involving the carotid bifurcation. As an adjunct to the pulse delay technique, McRae and Kartchner\textsuperscript{23} introduced a method for electronically amplifying and visualizing the frequency envelope of bruits heard in the neck. Criteria based upon the site of maximal amplitude and bruit duration within each cardiac cycle were used in a qualitative fashion to help localize and estimate the degree of narrowing of the carotid artery.

The second type of oculoplethysmography in current use is that developed by Gee et al.\textsuperscript{24} With this device, suction cups are placed over the sclera. A negative pressure of 300 mm Hg is applied simultaneously to both globes, which increases pressure in the eye and obliterates ocular pulsations. By gradually deflating the vacuum pressure, it is possible to note on a strip-chart recorder the point at which ocular pulses reappear. The relationship between the amount of vacuum applied at the point of pulse reappearance can be related both to the intraocular and systolic pressure in the ophthalmic artery.

Results. The reported accuracy of the pulse delay method with or without the adjunctive use of phonoangiography varies greatly. Since it will be impossible for this author to reconcile these differences, readers are urged to consult the published reports and draw their own conclusions. Our own group investigated this method and found it disappointing.\textsuperscript{25} We examined the results in 110 sides in which there was angiographic confirmation. The test was positive in all patients with total occlusions of the internal carotid artery, but in only 42% of those with a 50% to 99% diameter-reducing stenosis. Further, a positive test could not be used to distinguish between a high grade stenosis and complete occlusion, and phonoangiography was not a useful test either alone or in conjunction with the oculoplethysmography. In sharp contrast to our results are those reported by Kartchner et al.,\textsuperscript{26} that if the carotid artery diameter is narrowed by 40% or more, the accuracy of the test is consistent at a level approaching 90%.

The reported accuracy in detecting high-grade stenoses with the pressure measuring phlethysmographic system has been quite uniform. The major argument is the degree of diameter reduction at which the test will become positive. Gee et al.\textsuperscript{24} and others\textsuperscript{27} have used a diameter reduction of 65%. Clearly this system, by measuring systolic pressure indirectly, should have very few false positives if properly performed. A major limiting factor of this, as well as the other, indirect tests is their inability to detect and classify all degrees of involvement.

Direct Tests

Tests that derive their information directly from the carotid bifurcation are in this category; they involve a variety of methods currently in use and being evaluated at the present time. The technological advances both in instrumentation and signal processing are proceeding at such a rapid pace that this field is continually changing, making it difficult to predict what the future holds. It is the opinion of this reviewer that when the final chapter on this subject is written, one or more of these tests will be the most useful both in the clinical and research aspects of this critically important field.

Quantitative Phonoangiography. This method developed by Lees and Dewey\textsuperscript{28} demonstrated the feasibility of estimating the residual lumen diameter in the region of a plaque by a theoretical analysis of the sound produced by the vibrating arteries. The appli-
cates of such a method depends upon certain assumptions: the peak systolic flow velocity is consid-
ered constant and the break frequency of the bruit can be related to the effective diameter of the jet of
blood flowing through the stenosis. The bruit analy-
sis is done using a microprocessor to produce a
mean intensity spectrum. A 50 msec window is then
positioned over the bruit as seen on the cathode ray
tube at the location where the analysis is performed.
The computer performs a fast Fourier transform on
the spectra from six cardiac cycles over the window.
Once the break frequency is displayed on an oscillo-
scope and determined, the residual lumen diameter
at the site of stenosis is easily calculated using the
following formula (Figure 3):

\[ D = \frac{u}{f_0} \]  

(1)

where \( D \) = residual diameter (mm), \( u = 500 \text{ mm/sec} \), and \( f_0 \) = break frequency (Hz).

We examined the use of this system in 41 sides
with bruits that had angiographic correlation.29 There
was agreement within 1 mm in 85% of the bruits that
could be analyzed. The test is simple to apply in
practice, but does have limitations. Only about 20% of
the patients referred to our laboratory for study have asymptomatic bruits. Those patients who are
both symptomatic and have a bruit will constitute a
larger number, but at the moment it is not entirely
clear how to use the results of this test. Since the test
is accurate in predicting residual lumen diameter and
the results appear to be reproducible, it may be a
useful method of following disease progression in
those patients with a carotid bruit.

**Ultrasonic Arteriography.** Since Hokanson and co-
workers in 197130,31 demonstrated the feasibility of
using the Doppler effect to generate "flow images,"
there has been a rapid development of this method
for use both with continuous-wave and pulsed ultrasonic systems (Figure 4). The concept is basically
quite simple. When an ultrasonic beam is directed at
a blood vessel, it is possible to register flow at all
points where the velocity of the red cells produces a
frequency shift above 200 Hz, a level corresponding
to that frequency shift that occurs secondary to wall
motion. If the system is pulsed, thus taking advantage
of range gating, it is possible to discretely sample the flow from any point along the path of the
sound beam. This Doppler system, when combined
with a position-sensing arm attached to the trans-
ducer, permits the user to generate a two-dimension-
al image of all points within a blood vessel where flow
is occurring. The same type of study can be done
using a continuous-wave Doppler system but, when
used in this manner, the system has no depth
resolution.32,33

![Figure 3](http://atvb.ahajournals.org/) The break frequency of the bruit is indicated by the vertical line as displayed
on the oscilloscope. (From Knox R, Breslau P, Strandness DE Jr. Quantitative carotid
These methods were designed for use in the carotid system, with the hope that the generated flow image would correspond to that seen with contrast arteriography. A problem encountered early in their development was frequently finding calcification either in the wall of the artery or within the atherosclerotic plaque. Since calcium interferes with the transmission of sound, acoustical shadowing resulted. The acoustical shadowing produced a sonoluent area on the oscilloscope that prevented the user from determining if the calcium was present in the wall of the artery or in an underlying plaque. Because of these limitations, most investigators have used the flow image largely as a road map to identify the anatomy of the bifurcation and not as a method of estimating the degree of stenosis. However, Miles and colleagues developed a microprocessor-based system to generate an image from more than one position plane to estimate the degree of arterial stenosis.

The advantage of this approach is that, with the generated image of the carotid bifurcation, the technician is able to sample the flow from discrete points along and across the common, internal, and external carotid arteries. In addition, the method is accurate for verifying the presence of a total occlusion of the internal carotid artery. The use of the velocity patterns across the bifurcation to predict the degree of stenosis has gone through two phases. The first and still most widely used is audible interpretation of the detected frequency shifts. Since high-grade stenoses (greater than 50%) produce a marked increase in flow velocity through the narrowed segment (greater than 4 KHz using a 5 MHz system), this is recognized by listening alone. However, for detecting lesser degrees of narrowing, real-time spectrum analysis of the velocity patterns has benefits. Identification of the velocity changes associated with a 50% diameter-reducing stenosis depends upon the appearance of spectral broadening, which is secondary to the local flow disturbances produced by the lesion. The spectral changes used in practice will be considered in more detail in the next section.

The reported accuracy with either a pulsed or continuous-wave flow imaging system has been excellent for high-grade stenoses and total occlusions (greater than 90%). With lesser degrees of involvement, the results were initially poor when audible interpretation alone was used, but have improved with the addition of spectrum analysis.

Duplex Scanning. Because of the widespread use of real-time B-mode imaging in the heart, abdomen, and pelvis, it was only natural that this method would also be applied to the carotid artery. However, repeated experience has shown that the B-mode image alone is not satisfactory, and, for this reason, nearly every current system also uses a pulsed Doppler — thus the term "Duplex."

The reasons for the failure of the B-mode systems alone are as follows: 1) it is often difficult to deter-
mine with certainty the two branches of the carotid artery; 2) a thrombus has similar acoustic properties as flowing blood — thus total occlusions of the internal carotid artery are often missed (Figure 5); and 3) high-grade stenoses, which are often produced by plaques containing calcium, are difficult to accurately classify without the capability of assessing the velocity changes across the narrowed segment.

The major advantages of the combined echo-Doppler approach is that, with the image of the artery seen on the oscilloscope, it is possible to selectively sample the flow in any desired plane and point within the vessel (Figure 6). Since the sample volume size of the pulsed Doppler is small (∼3 mm$^3$ in the system we use), it is possible to examine flow not only at points along the artery, but also across it.

The successful use of spectral analysis of the velocity signals depends upon the association of specific velocity patterns with varying degrees of stenosis. This was first tested empirically by examining the recorded spectra from the common and internal carotid artery and comparing these with the radiologic estimates of the degree of narrowing. When this was done, certain patterns began to emerge which then could be tested prospectively (Figure 7).

At this point, it is necessary to briefly comment on the problems involved in estimating the degree of stenosis by even multiplanar arteriograms. Since the arteriosclerotic plaque varies in a random manner in both its transverse and longitudinal dimensions, it is not surprising that measurements of diameter reduction are less than precise. We investigated this prospectively by examining the intra- and interobserver variability in the estimation of the degree of stenosis by the radiologists involved in our studies. The variability in measuring the degree of stenosis was ± 20%. Even when the classification scheme was broken into five groups (normal, 0% to 15%, 16% to 49%, 50% to 99%, and occlusion) problems were still apparent. When these broader categories were used, the same reader agreed with himself on a second review of the films only 74% of the time.

We have chosen to use these five broad categories in evaluating the accuracy of scanning. The variables for classifying the degree of stenosis into these groups depend upon the recorded peak frequencies from the diseased area as well as the time of onset and degree of spectral broadening. After several validation studies, we decided to use the spectral criteria shown in Table 1. The sensitivity of spectral analysis now exceeds 95%. However, early in our studies, the specificity was low, approximately 38%. This was increased to 84% when we recognized the features present in the common carotid artery velocity patterns that were predictive of the state of the carotid bulb.

The application of such methods for the evaluation of the carotid bifurcation and internal carotid artery has proven useful in clinical practice. It is now clear that these methods can be an important screening tool.

![Figure 5. B-mode image of the common carotid artery. The prominent echoes from the anterior and posterior walls are easily seen. The line observed indicates the path of the Doppler beam, and the arrow indicates the position of the sample volume. This artery was occluded.](https://example.com/figure5.jpg)
Figure 6. Longitudinal scan of the common carotid artery (A) with the jugular vein (B) observed immediately anteriorly. The Doppler beam (white line) is positioned to permit sampling from the center of the artery. (From Fell G, Phillips DJ, Chikos PM, et al. Ultrasonic duplex scanning for disease of the carotid artery. Circulation 1981; 64:1191-1195, by permission.)

<table>
<thead>
<tr>
<th>Disease classification</th>
<th>Common carotid artery</th>
<th>Internal carotid artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal contour*</td>
<td>No or minimal spectral broadening in decelerating phase of systole; window still present</td>
</tr>
<tr>
<td>Minimal (1%-15%)</td>
<td>Abnormal contour</td>
<td>Minimal or even &quot;no&quot; spectral broadening in decelerating phase of systole; clear window</td>
</tr>
<tr>
<td>Moderate (16%-49%)</td>
<td>Abnormal contour</td>
<td>Spectral broadening throughout systole; no window; systolic peak &lt; 4 KHz</td>
</tr>
<tr>
<td>Severe (50%-99%)</td>
<td>Abnormal contour</td>
<td>Systolic peak &gt; 4 KHz; increased flow; marked spectral broadening</td>
</tr>
<tr>
<td>Occlusion</td>
<td>Flow to zero or reversed</td>
<td>No signal.</td>
</tr>
</tbody>
</table>

"Normal" means the first zero slope after systole occurs below the midslope. "Abnormal" means the first zero slope after systole occurs above the midslope.
Figure 7. Velocity patterns recorded from selected sites in the internal carotid artery.  
A. Normal. The flow is above zero with a clear area beneath the systolic peak.  
B. Velocity pattern seen with minimal disease (up to 15% diameter reduction). There is more widening at the systole.  
C. Velocity pattern associated with a 16% to 49% diameter stenosis. Most of the systolic window is lost.  
D. Velocity pattern associated with a greater than 50% stenosis. There is a peak frequency above 4 KHz with marked spectral broadening. (From Fell G, Phillips DJ, Chikos PM, et al. Ultrasonic duplex scanning for disease of the carotid artery. Circulation 1981;64:1191–1195, by permission.)
procedure for patients with suspected arteriosclerosis of the carotid bifurcation.  

The current ultrasonic scanning devices that use Doppler can also examine the subclavian and vertebral arteries. The origin and first few centimeters of the vertebral artery are relatively easy to visualize and to use for velocity readings. During a routine examination, the following facts are noted and recorded: 1) presence or absence of a signal; 2) direction of flow; and 3) change in peak velocity.

These methods have not been as useful in studying the vertebral artery as the carotid artery. This is largely because it is very difficult to identify vertebrobasilar disease with certainty and to relate the finding of a specific anatomic lesion to the clinical picture. In addition, it is very rare that patients with symptoms of vertebrobasilar disease do not also have very severe carotid artery disease. In fact, the use of the term "caroticovertebral" disease is a better description of the arteriosclerosis that involves the extracranial arteries. Perhaps with more experience we will be able to identify specific patterns of involvement that will permit a better understanding of that constellation of symptoms and signs currently attributed to the posterior circulation.

Diagnostic Methods Used In Evaluating the Peripheral Arterial Circulation

There are a variety of testing methods currently used to detect and localize the presence of arteriosclerosis. Most of these techniques are indirect (the variables examined are physiologic, not anatomic) and are used to detect alterations in the pressure and flow relationships at one or more sites in the limb.

The method most applicable to clinical practice is the indirect measurement of systolic pressures at one or more levels of the limb. 43-45 It is an established fact that the systolic pressure is normally amplified as the pressure pulse traverses the limb, i.e., the systolic pressure at the ankle should be higher than at the level of the upper arm. In practice, the ankle pressure is usually expressed as a ratio. This is referred to as the "ankle/arm index," which should be greater than 1.0. It is also feasible to measure pressures from the toes. In normal subjects there is a gradient between the ankle and the toes. The toe pressures should be 80% to 90% of the arm pressure.

If pneumatic cuffs are placed at the upper thigh above the knee, below the knee, and at the ankle, it is possible to measure the systolic pressure at each of these levels. 46, 47 The pressure at the proximal thigh normally exceeds the upper arm by 30 to 40 mm Hg. Since the intraarterial pressure at this site normally equals brachial artery pressure, this higher level represents cuff artifact. Even given this fact, the pressures can be useful if certain rules are followed: 1) pressures measured from both thighs should be within 20 mm Hg of each other; 2) differences greater than 20 mm Hg between two cuff levels is suggestive of occlusive disease in the intervening segment; and 3) the upper thigh pressure index should normally exceed 1.2. Values below 0.8 are usually indicative of complete occlusion proximal to the cuff. 48

The pressures at each level of the limb can be measured using a continuous-wave Doppler device, 49 a mercury strain gauge plethysmograph 50 or the photoplethysmograph. 51 The sensing site is either the tibial arteries (Doppler) or the toes (plethysmograph). These devices are used to sense the point at which flow is restored during cuff deflation.

With the development of the ultrasonic velocity detector, it became feasible to qualitatively assess the velocity patterns from the major arteries of the upper and lower extremity. 49-51 These devices may be purchased as a pocket-sized unit for use with stethoscope ear phones or a more sophisticated type able to detect changes in flow direction. The latter may be used with a zero-crossing detector to provide analogue tracings of the arterial velocity patterns on a strip-chart recorder. Arterial blood flow in the arteries of the lower limb under resting conditions is normally triphasic. The three components include forward flow during systole, transient reverse flow in early to middiastole, and a small forward flow component in late diastole. With the development of arteriosclerosis, this velocity pattern is dramatically altered. The reverse and late forward flow components disappear so that the entire pulse cycle is represented by a monophasic signal that never reaches the zero-flow point. These flow patterns can be audibly recognized by a trained observer, but a permanent record is usually taken for future comparisons.

To objectively characterize the changes that occur secondary to arteriosclerosis, some investigators have attempted to define measurable features from the recorded velocity patterns. Gosling and coworkers 52, 53 were the first to describe a pulsatility index based upon the Fourier amplitudes of the maximum instantaneous velocity. This ratio, which can be measured from single or averaged waveforms, has the advantage of being independent of the angle of the Doppler probe relative to the artery. The calculation involves the following equation:

\[
Pulsatility\ index\ (PI) = \frac{\text{peak\ to\ peak\ velocity}}{\text{mean\ velocity}}
\]  

The major application of this method has been for the evaluation of the aortoiliac segment. The normal femoral artery PI is in the range of 4–13. 54 Any value below 4.0 may be associated with significant stenoses proximal to the inguinal ligament. A major criticism of this method is that a femoral artery PI of less than 4.0 may also be seen in the presence of superficial femoral disease. 55-57 Our work confirmed this latter observation, but the determination is still clinically useful if a femoral PI of > 4.0 is found. Under these circumstances, the likelihood of having hemodynamically significant disease proximal to the inguinal ligament is less than 10%. 
Because of the clinical importance of indirectly assessing the hemodynamic status of the aortoiliac segment, numerous other methods have been developed and tested. These include the measurement of transit times and the $T/2$ of the mean femoral artery velocity recovery time following reactive hyperemia.57-59 These methods have not gained widespread application because they are somewhat cumbersome to use and have the same limitations as the pulsatility index.

Skidmore and Woodcock60 developed a mathematical solution to the femoral artery velocity waveform, which uses a third-order Laplace transform whose coefficients are related to distal impedance, proximal lumen diameter, and vessel stiffness. This method, which requires computer waveform analysis, may allow recognition of iliac artery stenoses greater or less than 50%. It has not yet been evaluated for usefulness by other centers.

A useful adjunct to the measurement of ankle blood pressures has been the addition of stress by either treadmill exercise or reactive hyperemia produced by cuff occlusion at the thigh level. These maneuvers will markedly increase limb blood flow, which in turn may increase the pressure drop across stenotic segments, making it possible to detect disease that does not produce pressure or flow abnormalities at rest.59 Exercise is at a low workload of 2 mph on a 12% grade either to claudication or until 5 minutes has elapsed.61-63 Normally at this low workload, the ankle systolic pressure after exercise remains above 80% of the baseline and returns to the pre-exercise level in less than 3 minutes. Since the extent of the pressure drop and its recovery time reflect the amount of ischemia and the extent to which the collateral circulation is developed, this stress test is useful for estimating the functional impact of arteriosclerosis on the limbs. The values in common use for the various tests covered in this section are shown in Table 2.

Cost Effectiveness of Diagnostic Methods

With the rising cost of medical care, the addition of new diagnostic tests must be justified whenever possible. This is often difficult, as a test may become part of the patient workup and is not essential for arriving at a definitive decision. The task is easier in those circumstances in which the test results alter the further evaluation or therapy. One area where this issue can be examined is in patients with suspected carotid disease but who are asymptomatic.

Extracranial Arterial Circulation

Patients in this category usually present with a cervical bruit and constitute about 20% of the patients referred to the laboratory for study. While there is some disagreement in the medical community concerning the management of these patients, most physicians would agree that patients in the following categories would not be subjected to arteriography if this information were available from a noninvasive test: 1) patients with a normal carotid bifurcation; 2) those with occlusion of the internal carotid artery; and 3) those with stenoses that narrow the carotid bifurcation by less than 50%.

Previous studies from this laboratory have shown that approximately 30% of asymptomatic patients with cervical bruits will have a greater than 50% diameter-reducing lesion as the cause for the bruit.41 This group is of most interest since these patients are thought to be at greatest risk for stroke. Whether this is, in fact, the case remains to be proven.

Given these considerations, is it reasonable and cost effective to use ultrasonic duplex scanning as the definitive screening test before performing arteriography? To test this, the following facts must be taken into account: 1) ultrasonic scanning is 95% sensitive and 84% specific; 2) the cost of an ultrasonic scan, including physician interpretation, is approximately $150.00; 3) the cost of a standard arterio-

Table 2. Summary of Values in Common Use

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle pressure</td>
<td>Normal = brachial</td>
</tr>
<tr>
<td>Ankle pressure index</td>
<td>Normal &gt; 1.0; hemodynamically significant lesion &lt; 0.95</td>
</tr>
<tr>
<td>Ankle pressure after exercise</td>
<td>Normal &gt; 0.80 of baseline; return to baseline within 3 minutes</td>
</tr>
<tr>
<td>Proximal thigh pressure</td>
<td>Normal &gt; brachial</td>
</tr>
<tr>
<td>Proximal thigh index</td>
<td>Normal &gt; 1.2; iliac stenosis 0.8-1.2; iliac occlusion &lt; 0.8</td>
</tr>
<tr>
<td>Toe pressure</td>
<td>Normal = 80% to 90% of brachial</td>
</tr>
<tr>
<td>Toe indices</td>
<td>Normal = 0.8-0.9; hemodynamically significant lesion &lt; 0.60; rest pain, often &lt; 0.15</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>Normal femoral 4-13, mean 6.7</td>
</tr>
</tbody>
</table>
gram is estimated to be about $1,000.00, which is probably low when the cost of hospitalization is included; 4) the projected cost of an intravenous arteriogram is extremely variable but it is assumed to cost one-half the standard procedure; and 5) published reports on intravenous arteriography suggest that somewhere between 10% and 20% of the studies are totally inadequate due to motion artifact. (For this comparison, a figure of 10% will be used.)

The cost of the following approaches for 100 patients with cervical bruits is as follows:

1. Conventional arteriography alone = $100,000.
2. Intravenous arteriography alone = $50,000. If we assume that 10 studies would be unsatisfactory and require conventional arteriography, this would increase the cost of this approach to $60,000.
3. Ultrasonic screening = $15,000. Since 30 patients would be suspected of having a greater than 50% stenosis and require arteriography, an additional $30,000 in cost would be added giving a total cost of $45,000. If the ultrasonic study were followed by an intravenous arteriogram, the total cost would be $30,000.

If this analysis is correct, then it would appear that preliminary screening before arteriography is cost-effective. However, these assumptions do not take into account the errors that might occur with the ultrasonic studies. Based upon our current results, the following types of errors might be expected:
1) 1% of patients with a high grade stenosis would be called occluded; 2) 5% of patients with a diameter reduction stenosis of less than 50% would be placed in the greater than 50% category; 3) 8% of patients with a stenosis of greater than 50% would be classified as having a lesser degree of narrowing.

We cannot tell whether these misclassification errors are serious enough to warrant arteriography in all patients because we now lack solid data on the subsequent risk for stroke in these patients.

Peripheral Arterial Circulation

A similar analysis for the cost effectiveness of noninvasive studies for the peripheral arterial problems is much more difficult. In most instances, the noninvasive tests are used to complement the physician's clinical impressions and provide some objective measure of the state of disease. For example, the measurement of the ankle/arm index will provide objective confirmation of either disease progression or improvement in collateral artery function. In some circumstances, this may prompt a more aggressive surgical approach to the patient's problem, but this is difficult to express in terms of cost savings to the patient.

Research Applications

Clinical research in the field of arteriosclerosis has always been hampered by the lack of objective, noninvasive methods both to detect the presence of the disease and to follow its progression. The requirements for such methods are much more stringent than for the evaluation of a patient with symptoms and signs of the disease. An important fact is that, with few exceptions, the patient who presents with the clinical manifestations of the disease has advanced, complicated plaque as the underlying cause. Thus, in most patients we are studying the disease at a late and irreversible stage in its progression.

For the present and the future, the application of noninvasive techniques can be thought of in two separate, distinct ways. The first and simplest is the patient-based study in which the testing procedures are used to assess the natural history with and without therapy. The second is a population-based survey in which the prevalence of disease is unknown but is important in terms of assessing the role of potential risk factors.

Ideally, any test should be applicable to every study population, but such is not the case. For example, if the target population is known to have a high prevalence of disease, then the test must have a high sensitivity. In this situation, it is better to tolerate a small percentage of false negatives. An example of this is in screening patients suspected of having carotid disease. Since the patients have all been initially seen by a physician, it is expected that the prevalence of disease is high, and in fact it is. Since Duplex scanning has a sensitivity of over 95%, the number of false positives has consistently been below 5%.

On the other hand, for a population with a predictably low prevalence of disease, it is more important to have a test with a high specificity, i.e., very few false positives. The evolution of the ultrasonic Duplex scanner illustrates this problem quite well. Initially, the specificity of this test was only 38% — thus, we would wrongly predict that disease was present in 62% of a normal population. While the errors were not in predicting high-grade stenoses, they reflected our inability to separate normal subjects from patients with minimal degrees of narrowing. However, with experience and the addition of new algorithms shown in Table 1, the specificity has increased to 84% while not sacrificing sensitivity. Thus, we now have a noninvasive test that may be used for nearly all study populations.

However, even a test with a high sensitivity and specificity is not necessarily suitable for longitudinal studies. As noted earlier, a test that provides a simple yes-no answer is of limited value for this purpose when it is positive. This is certainly true if the test is used as part of an intervention trial to document the effect of therapy on disease progression.

It would be more reasonable to adopt a test that classifies disease into rather broad categories of degrees of narrowing and establishes the diagnostic confidence limits for each group. The reason for the broader categories is that we know that even the current gold standard arteriography poses problems concerning observer variability. Thus, we have attempted to develop algorithms for classes of steno-
s. i.e., 10%–49%, 50%–99%, so that if a patient does move from one category to another, we can be much more confident of the test results.

Since classification of stenosis category using the algorithms in Table 1 is still largely subjective, we have begun to use computer-based systems to analyze the spectral patterns. The assumptions made were as follows: 1) the data are taken from representative sites in the artery; 2) the pressure-flow relationship for varying degrees of disease are relatively constant; and 3) there are specific features, patterns, or combinations thereof that are specific for the diagnostic categories chosen. Preliminary results indicate that these assumptions are, in fact, true and by using pattern recognition programs, a computer can classify spectra for each of the diagnostic categories currently in use with a high degree of accuracy.

Finally, with regard to carotid arteriosclerosis, an important fact is beginning to emerge, namely, that disease progression defined solely as increasing narrowing is not synonymous with clinical outcome. How could this be? It simply means that the biological behavior of the plaque is probably more important than the degree of stenosis. The key question as to why a plaque loses its surface continuity and becomes a nidus for thrombi will not be answered by examining the degree of stenosis alone. Very high resolution B-mode scanning may be able to examine the surface characteristics of the plaque and answer some of these questions, but the problem is not a trivial one.

With regard to the lower limbs, the challenges are somewhat different. Here, there is little question that disease progression can be monitored by changes in perfusion pressure. Thus, a fall in the ankle/arm index of more than 0.15 (range of measurement variability) is due either to disease progression or thrombosis on preexisting plaques. On the other hand, a rise in the index cannot be equated with plaque regression since any improvement in collateral flow will raise distal pressure. However, it is important to recognize that the index will never rise to a level higher than that before the development of progression.

A great advantage of the limb blood pressure tests is that they remove observer bias and problems associated with the detection and grading of peripheral pulses. These simple tests also lend themselves to studies of large patient populations by technologists. The results of such testing also permit a numerical grading of the degree of involvement, which is not possible by clinical evaluation alone.

Finally, it would be ideal if there were a specific segment of the arterial system that could be used as the reference artery for both prevalence and natural history studies. Unfortunately, there is no such segment since it appears that both the prevalence of disease and the identified risk factors vary from one region of the arterial system to another. For example, our own prospective studies in diabetics have shown that cigarette smoking is a very potent risk factor for the development of arteriosclerosis in the limbs but not in the development of carotid artery stenosis. This important fact must be kept in mind for prospective studies.

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Noninvasive evaluation of arteriosclerosis. Comparison of methods.
D E Strandness, Jr

doi: 10.1161/01.ATV.3.2.103

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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