CARDIOVASCULAR DISEASE IN AMERICAN INDIANS (PHASE III)

OPERATIONS MANUAL - VOLUME SIX

SPECIAL STUDIES
CAROTID ULTRASOUND AND TONOMETRY

THE NATIONAL HEART, LUNG AND BLOOD INSTITUTE
OF THE NATIONAL INSTITUTES OF HEALTH
THE STRONG HEART STUDY

Cardiovascular Disease in American Indians (Phase III)

Operations Manual

Volume Six

Special Studies
Carotid Ultrasound and Tonometry

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VOLUME VI

SPECIAL STUDIES
CAROTID ULTRASOUND AND TONOMETRY

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STRONG HEART STUDY
ULTRASOUND READING CENTER MANUAL OF OPERATIONS

A. Goals of the Study: Carotid arterial ultrasonography and arterial pressure waveform analysis permit non-invasive assessment of arterial hypertrophy, detection and quantification of atherosclerosis, and estimation of arterial stiffness and hemodynamics. These methods will be used in Phase III of the Strong Heart Study to accomplish the following specific aims:

1. Determine the distributions of carotid arterial wall thickness and atherosclerosis in American Indians and compare them to findings in other ethnic groups.

2. Assess the distribution of arterial stiffness in American Indians and the relations of arterial stiffness to: a) concurrently measured arterial hypertrophy, atherosclerosis and risk factors and b) echocardiographic measures of left ventricular structure assessed previously during SHS phase II.

3. Determine the impact of diabetes, impaired glucose tolerance and insulin resistance on arterial structure and function in American Indians.

4. Examine the relation of elevated blood pressure and treated hypertension to arterial hypertrophy, atherosclerosis and arterial stiffness in American Indians.

5. Determine the relations of adipose and fat-free body mass and their distribution (waist-hip ratio) to arterial hypertrophy, atherosclerosis and stiffness in American Indians.

6. Determine the phenotypic heritability of arterial wall thickness, atherosclerosis and arterial stiffness in American Indian sibships and extended families.

B. Background of the Study:

Findings in Phases I and II of the Strong Heart Study identify its participants as a population of unusual interest with regard to studying the biology of cardiovascular disease. The overall prevalence of diabetes is high, with age-adjusted prevalence rates ranging from 33% among male SHS participants in North/South Dakota to 73% in female Arizona participants. Similarly, the degree of obesity (mean body mass index =31.5±6.5 kg/m² in SHS women and 29.8±5.9 kg/m² in SHS men) is much greater than in the overall U.S. population (1). Strong Heart Study participants in Arizona and Oklahoma have prevalences of hypertension (by application of JNC-V criteria to standardized single-visit blood pressures) comparable to NHANES III data for the general U.S. population, whereas hypertension prevalences in the Sioux (28% in women and 27% in men) were lower. Notably, 55% and 53% of hypertensive SHS men and women were both treated and had controlled blood pressure, exceeding the respective 46% and 51% general U.S. rates of successful management of hypertension. Of particular biologic interest, dyslipidemia was relatively uncommon, with mean total cholesterol concentrations about 20 mg/dl lower in SHS men and 40 mg/dl lower in SHS women than national mean values for the same age group despite the higher relative body weight in our subjects (1-2).

Despite the relatively low prevalence of uncontrolled hypertension and lack of extremely elderly subjects (>80 years), high prevalences of increased left ventricular mass (19% had values above the prognostically-validated partition value of 51 g/m²²) and ejection fractions <40% (nearly 3%) were revealed by the echocardiographic data from the first 3,121 Phase II
participants to have their studies processed. The high total mortality in Strong Heart Study communities -- ranging up to twice the rates in U.S. whites among 45 to 64 year-old Indians (2a) -- and substantial contribution thereto of cardiovascular death indicates that the different mix of risk factors and evidence of target organ damage than in other populations is not associated with a benign cardiovascular prognosis. This makes the Strong Heart Study population an ideal one in which to evaluate whether standard risk factors retain the same relative strength for prediction of subsequent cardiovascular events and for the presence of concurrent preclinical target organ disease as in models derived from predominately Caucasian or urban populations with very different risk factor distributions. In addition, the large family size of Strong Heart Study participants facilitates sib-pair analysis of phenotypic inheritance, permitting identification of heritability of arterial abnormalities in the SHS Family Study, as has already been found for echocardiographic variables measured during Phase II.

C. Arterial Evaluation:

Carotid Ultrasound: Recent progress has made available non-invasive methods to evaluate arterial structure and function. Ultrasound measurement of carotid wall thickness (combined intimal-medial thickness) has been validated using gross and histopathologic reference standards (3-5) and has been found to be highly reproducible (5-9). Ultrasound scanning of the carotid arteries gives precise measures of structure (3-4), detects atheromatous plaque (3,10-12) and, in population-based studies, has proven to be a powerful noninvasive tool for the prediction of subsequent morbid events (10,13,14). Two large U.S. epidemiologic studies involving over 10,000 subjects, the Atherosclerosis Risk in Communities (ARIC) study (15) and the Cardiovascular Health Study (16), have provided carotid artery measurements in black and white men and women over a broad age range and will permit comparison of distribution of wall thickness and prevalence of atherosclerosis in American Indians with these populations.

The presence of carotid arterial abnormalities is strongly correlated with coronary atherosclerosis (17-20). In fact, both carotid atherosclerosis and carotid wall thickness were predictors, independent of standard risk factors, for the development of subsequent myocardial infarction in the Kuopio Heart Disease Risk Factor Study (11,13,21). For each 0.1mm increase in common carotid artery intimal-medial thickness, the risk of myocardial infarction increased by 11% (13). In the Cardiovascular Health Study common carotid artery wall thickness was found to be an independent correlate of both prevalent coronary heart disease and stroke (16). In keeping with these observations, carotid wall thickness and/or prevalence and severity of atherosclerosis have been found to correlate with cardiovascular risk factors such as smoking (22-25), serum lipids (25-27) and diabetes mellitus (28). Furthermore, data from our laboratory have identified ultrasound evidence of carotid hypertrophy as at least as sensitive a marker of end-organ damage as is echocardiographic left ventricular (LV) hypertrophy in hypertension (6,29).

Another strong advantage of this technique is the high prevalence of abnormalities which are likely to be detected, increasing the ability of the study to detect the influence on the circulation of diabetes, obesity and other risk factors that are prevalent in American Indians. In the Cardiovascular Health Study (all subjects ≥65 years), 75% of men and 62% of women were
found to have some degree of carotid atherosclerosis, although significant stenosis was uncommon (16). In the Kuopio Heart Disease Risk Factor Study involving 412 men aged 42 to 60 years, 49% had some abnormality of carotid anatomy (30). Among a subset of 100 men followed for two years, some progression of disease was noted in 83 and was correlated with smoking habits but not serum lipids at baseline (31). Among 517 French women aged 45-54 years, Bonithon-Kopp et al. detected intimal-medial thickening in 30% and plaque in 8.7% (25). Ultrasound measurement of the common carotid artery intimal-medial thickness has also been used as the primary endpoint in assessing efficacy of lipid-lowering therapy (32,33), with computer image processing permitting the detection of wall thinning over a two-year period in as few as 50 subjects (20).

Several approaches to the measurement of carotid wall thickness and quantification of atherosclerosis have been employed in previous studies, using either discrete measurements of specific segments (6,15,16,20,34) or scoring systems derived from measurements at multiple sites (12,19). Protocols have included measurement of both near and far wall thicknesses (16,19) or have been limited to far wall thickness (6,15,20,28,34). As experience and analyses have accumulated, several observations have emerged. It is apparent that measurement of the far wall intima-media complex is more accurate than that of the near wall. There is systematic encroachment of the adventitial acoustic signal into the media and of the intimal acoustic signal into the lumen of the near wall, whereas encroachment of the intimal acoustic signal into the medial of the far wall is irrelevant since the combined intima-media complex is being measured. Thus it has been suggested that investigators measuring and incorporating near wall thickness also provide separate measurements of the far wall for comparability with other studies (35).

Secondly, the optimal imaging plane is one wherein the transducer beam is perpendicular rather than oblique to the structure of interest. Thus the parallel walls of the tubular common carotid artery are more crisply imaged than those of the carotid bulb (28) resulting in much higher measurement yield and reproducibility of common carotid artery intimal-medial thickness than of the bulb or internal carotid artery (9,15,36). In fact Crouse has recently reported a yield of only 78% for measurement of internal carotid artery wall thickness (36).

Because of flow dynamics the common carotid artery is much less susceptible to discrete atherosclerosis than are the bulb and proximal portion of the internal carotid artery (37) indicating that intimal-medial thickening of various segments may have different pathophysiologic implications and mechanisms (27). Although it has been proposed that diffuse intimal-medial thickening may represent "early" atherosclerosis (15,27), there remains considerable controversy in this regard (35), and the interpretation of findings may also be influenced by the study population, i.e., the predominance of one or another cardiovascular risk factor. Although common carotid artery wall thickening may or may not represent early atherosclerosis, common carotid wall thickness itself clearly relates to the risk of associated coronary atherosclerosis (11,13,16,20,21). These latter considerations support an approach which separates measurement of wall thickness and discrete plaque rather than deriving a score from combined maximal and/or average measurements.

Intimal-medial thickness has traditionally been measured from B-mode, or two-dimensional, images. Although we have made plaque measurements from B-mode images, we have utilized M-mode ultrasound images for measurement of lumen diameter and wall
thicknesses for several reasons. Two-dimensionally-guided M-mode images provide the same spatial resolution as B-mode images but add substantially higher temporal resolution thereby providing two major advantages to measurement from B-mode images. First, there is a significant decrease in intimal-medial thickness during systole concomitant with the increase in lumen diameter (38). Thus lack of ECG-gating and/or the limited temporal resolution of B-mode images will result in systematic underestimation of intimal-medial thickness. Secondly, a higher temporal resolution is mandatory if one additionally wishes to estimate vascular stiffness (as described below).

In consideration of the foregoing, the proposed study will measure far wall thickness of both common carotid arteries in addition to minimum and maximum lumen diameters from M-mode images. Discrete carotid atherosclerosis will be measured both qualitatively and quantitatively from the two-dimensional and Doppler studies (as described in detail in the Methodology section).

**Arterial Function:** In contrast to the anatomic view of arteries as static conduits, *in vivo* ultrasonography reveals pulsatile expansion of arteries during systole that transiently accommodates much of the blood ejected from the heart. The degree of arterial expansion (vascular strain) is, in turn, affected by age and disease states. The addition of sophisticated, non-invasive measures of arterial compliance which we have already applied in other, predominately white or African-American normotensive and hypertensive populations will permit a careful examination of the influences of diabetes, hypertension and other cardiovascular risk factors on vascular functional properties.

A high-fidelity solid-state non-invasive transducer, manufactured by the Millar Corporation, has recently been FDA-approved and made commercially available. The transducer functions as an applanation tonometer (39) and produces arterial pressure waveforms which are virtually indistinguishable from those obtained using invasive solid-state transducers. Accuracy of the transducer has been widely validated (40-43). The application of catheterization-validated transfer functions (44) to a radial artery pressure waveform obtained using applanation tonometry allows accurate determination of central aortic pressure and reconstruction of the central aortic pressure waveform as demonstrated by simultaneous intra-arterial catheters (45). Whereas previous estimates of arterial stiffness (or its inverse, compliance) were limited to selected subjects undergoing invasive evaluation or, when derived non-invasively, were subject to the confounding influence of distending pressure, applanation tonometry combined with ultrasound measurement of vascular pulsatility provides a powerful noninvasive tool to assess vascular function on an epidemiologic scale. Furthermore, the ability to measure wall thickness and the development and validation of a pressure-independent measure of arterial stiffness (to be described in detail in the Methodology section) represent substantial methodologic advances.

Arterial imaging and Doppler ultrasound evaluation in combination with noninvasive arterial pressure waveform recording provide three distinct bioassays: (1) carotid wall thickness in an area (common carotid) relatively spared by atherosclerosis as a measure of arterial hypertrophy and/or generalized atherosclerosis, with high yield and reproducibility; (2) detection of discrete atheromas (usually within the carotid bulb or proximal branch vessels) and grading of atheroma size or lumen stenosis as unambiguous measures of atherosclerosis; and (3) measures
of arterial stiffness in the carotid artery and in the entire arterial circulation. This makes it possible to identify the relations of the separate components of arterial disease (atherosclerosis, hypertrophy, stiffness) to cardiovascular risk factors, cardiac structure and function, and to prevalent and incident cardiovascular morbidity and mortality.

D. Progress Report/Preliminary Studies:

**Carotid Ultrasound Studies at the Cornell laboratory:** Carotid ultrasound studies to determine vascular structure and to detect atherosclerosis have been performed by the Cornell laboratory in combination with simultaneous echocardiography in over 800 subjects participating in ongoing studies (6,29,34,46-48). In half these subjects the arterial pressure waveform from one carotid artery has been recorded using a Millar solid-state high-fidelity external pressure transducer as an application tonometer (41) simultaneously with imaging of the contralateral carotid artery. Calibration of the application tonometry recordings for the mean brachial artery pressure yields calibrated instantaneous carotid pressures which, when combined with simultaneous carotid dimensions, provide estimates of arterial compliance. Experience to date demonstrates that this approach provides reproducible results (6).

Use of this methodology has permitted initial descriptions of several aspects of vascular structure and function in both hypertensive and normotensive populations studied in our laboratory. We have detected substantially higher intimal-medial arterial thickness in healthy asymptomatic hypertensive subjects compared to age- and gender-matched controls (6,29) and provided the first description of parallel increases in cardiac and vascular structure in hypertension (6). This finding has been subsequently validated in numerous other populations (5,49-52). The presence of visible atherosclerotic plaques was associated with left ventricular hypertrophy (LVH), independent of blood pressure, lipids, or other standard risk factors (34), providing a potential mechanism for the observed increase in vascular events, including stroke, in the setting of LVH (53). We have found vascular, in addition to cardiac, structure to be similar in 'white coat' hypertensives to that in normotensives in contrast to evidence of hypertrophy in sustained hypertensives (54), suggesting that 'white coat' hypertension is not associated with target organ damage and may have a benign prognosis. In contrast, individuals with 'white coat normotension' (normal clinic blood pressure with elevated ambulatory blood pressure) have vascular hypertrophy and atherosclerosis comparable to that seen in sustained hypertensives (55), an observation which may provide insight into cardiovascular morbidity in ostensibly normal individuals.

Our approaches to the estimation of arterial compliance have indicated that compliance is reduced in hypertensives at their operating level of pressure, but that these differences are substantially related to the level of distending pressure and structural adaptation by vascular hypertrophy (46). Furthermore, the shape of the arterial pressure waveform as manifested by a higher augmentation index is related to higher left ventricular mass, independently of age, gender, body size or the level of mean arterial pressure (47).

We are currently in the process of applying these same methodologies in two intervention trials to determine the impact of pharmacologic therapy (with an ACE inhibitor, a calcium channel blockers and a thiazide diuretic) on arterial structure and function, in addition to left
ventricular structure and geometry, and, ultimately, clinical outcome. In addition, we have recorded the radial artery pressure waveform using the Millar applanation tonometer with analysis provided by the SphygmoCor System which will be used in SHS Phase III to derive central arterial pressure waveforms that closely resemble those obtained by the more skill-dependent procedure of applanation of the carotid artery. Subjects studied in the Cornell laboratory include white and African-American normotensive and hypertensive subjects for comparison with SHS findings.

E. Research Design and Methods

**Carotid Artery Structure and Atherosclerosis:** Methods will be adapted from those used and refined at Cornell since 1989 and subsequently applied at other sites in multi-center studies (see Table 1). Imaging of both carotid arteries will be performed using Acuson 128 systems equipped with a 7 MHZ linear array arterial imaging transducer and previously-described methods (6,46). B-mode scanning of the right and left extracranial carotid arteries will be done in multiple projections to optimize the detection of discrete atheromata, identified on two-dimensional images as the presence of a discrete plaque at least 50% greater than the surrounding wall within any segment of either carotid artery (3,10,30). Carotid atherosclerosis identified in this way has been shown to correlate strongly with coronary artery disease (17-20) and risk of subsequent myocardial infarction (11,13,16). Carotid plaque size is quantified by computer-assisted measurement of plaque thickness on two-dimensional frames. The maximum diameter of the plaque is measured along with percent encroachment of the lumen diameter. Whenever lumen stenosis is significant (>50%) on the imaging study, the severity of stenosis is quantified using standard Doppler techniques (56). Peak flow velocities in the 1.5 to 2.5 m/sec range are indicative of 50-74% lumen stenosis whereas velocity in excess of 2.5 m/sec is indicative of >75% stenosis (16). Two-dimensionally-guided M-mode tracings of both the right and left distal common carotid artery approximately 1 cm proximal to the bulb are obtained to measure carotid wall thickness at end-diastole and lumen diameter at end-diastole (minimum diameter) and peak-systole (maximum diameter).

At the Reading Center, suitable frames for measurement are acquired in real-time from the videotape using a frame-grabber (Imaging Technology, Inc., Woburn, MA) interfaced with a high-resolution (480 x 640 pixel field) video monitor and stored on diskettes (Table 2). Following calibration for depth, the end-diastolic wall thickness (combined intimal-medial thickness of the far wall) and end-diastolic and peak-systolic internal diameters (by continuous tracing of the lumen-intima interface of the near and far walls) are measured on several cycles using electronic calipers and averaged. The ultrasound characterization and measurements of carotid wall layers has been validated by Pignoli et al (3) using gross and histopathologic reference standards. Measurement of carotid wall thickness is never made at the level of a plaque (infrequent in the common carotid artery).

**Carotid Artery Function:** Carotid artery function will be assessed using information derived from pressure waveforms acquired using applanation tonometry of the radial artery. Following completion of the carotid ultrasound study, brachial blood pressure will be measured in triplicate and averaged. The necessary information required for the SphygmoCor system will
be entered: SHS number (under patient ID), family name, first name, date of birth, social security number (under patient code), brachial blood pressure, and operator ID. The radial artery pressure waveform will be acquired with computer-generated derivation of the central pressure waveform using a transfer function. The information generated by the program is depicted on the attached sample report (see last page of manual). The relevant information for the principle measures of arterial function includes central blood pressure (to be used in regional compliance estimates [see Table 4]) and augmentation index. The additional parameters (excluding the pressure waveform) will be electronically transferred to the main database. The waveform raw data may be extracted separately for future analyses.

F. Ultrasonographer Training and Quality Control:

Arterial ultrasonography training, reading procedures and quality-control will be similar to those successfully employed for echocardiography in Phase II of the Strong Heart Study. Sonographers in the geographic locations will be identified and their credentials verified. One week of training will be provided at the Cornell Reading Center. Sonographers will observe the technique for the carotid ultrasound study as performed by a full-time research ultrasonographer with over 15 years of experience in research echocardiography and 7 years of experience with the carotid research protocol. Dr. Roman will demonstrate use of the applanation tonometer. All sonographers will be observed and critiqued in their performance of arterial imaging and in use of the applanation tonometer. In addition, a specialist from PWV Medical, the supplier of the applanation tonometry system and software (SphygmoCor) will visit each site to install and demonstrate the system and further instruct the sonographer in its use. Sonographers will complete worksheets at the completion of each study which can subsequently be utilized for written or oral feedback.

Copies of videotapes will be made and kept at the field sites to facilitate feedback and prevent loss of tapes. Initial readings will be performed by the research sonographer and verified by the physician-investigator. The initial and verification readings of the ultrasound studies will be performed in a blinded manner and then merged with demographic descriptors for final quality-control check of extreme values. Measurements will be performed using established in-house custom measurement and database and statistical analysis programs, including computer support from the Clinical Research Center. Data will be electronically transmitted to the Coordinating Center. Clinical alerts, such as high-grade stenoses, will be immediately reviewed and results relayed by FAX immediately to the Field Center.
TABLE 1: CAROTID ULTRASOUND PERFORMANCE PROTOCOL

Instrumentation: Ultrasonographs will be calibrated against a phantom at installation and at regular intervals thereafter; sonographers should verify that this is performed by Acuson as part of routine maintenance. The 7.0 Mhz vascular probe will be set to default with processing curves and a persistence setting optimal for imaging of the carotid artery (1/C/7). The usual depth is 30 to 40 mm.

Patient Preparation: Imaging is performed in a slightly darkened room with the subject in a supine position with slight hyperextension of the neck (a roll under the neck is optional) and lateral rotation, as necessary. Electrodes are placed for a modified three-lead electrocardiogram. The last name of the subject, first initial and SHS number should be entered before beginning the imaging study. In addition, the arterial system being imaged (left vs. right) should be entered on the screen.

Two-Dimensional Imaging and Doppler Study: Two-dimensional (B-mode) long-axis imaging from multiple planes (posterior, lateral, anterolateral) should be done to maximize detection of discrete plaque. Following identification of the carotid bulb, the transducer should be moved caudally to examine the common carotid artery until its origin from the aortic arch (left) or innominate artery (right). Both branch vessels should be scanned in a cephalad direction until their disappearance. Identifying features of the internal carotid artery on the imaging study include its larger size and motion away from the transducer as it proceeds intra-cranially, whereas the external carotid artery is usually smaller and has extracranial branches. Pulsed Doppler analysis should also be performed to identify distinguishing characteristics of the internal and external carotid arteries: the low resistance internal carotid artery is characterized by spectral broadening and persistence of flow during diastole whereas the high resistance external carotid artery has a rapid deceleration to the baseline with minimal diastolic flow. Extensive imaging of the bulb and proximal bifurcation should be performed given the high predilection for plaque in these regions. If plaque is present, the cine function should be activated to allow frame-by-frame scrolling to obtain the maximum plaque diameter. Electronic calipers should be used to measure maximum plaque diameter (mm) and, if possible, vessel diameter (mm) at the level of the plaque and diameter reduction (%). The transducer should then be rotated to obtain a cross-sectional image identifying the maximum incursion of the plaque into the lumen and plaque diameter, vessel diameter at the level of the plaque and diameter reduction of the lumen should again be measured using the cine function. Maximum plaque diameter from either of these views should be recorded on the Sonographer Worksheet based on plaque location. Addition of color flow to the cross-sectional image may aid in distinguishing plaque from lumen and in wall detection. If the plaque occupies a substantial percentage of the lumen area (>50%), pulsed Doppler analysis (with angle correction, if appropriate) should be performed to quantify the degree of stenosis by obtaining the peak velocity distal to the obstruction (1.5 to 2.5 m/sec = 50-74% obstruction, >2.5 m/sec = ≥75% obstruction).
M-mode Study: Following completion of the two-dimensional scanning protocol, the transducer should be positioned for optimal visualization of the distal common carotid artery perpendicular to the transducer beam (parallel to the linear probe). The M-mode cursor should be placed perpendicular to the long-axis of the distal common carotid artery to intersect the intima-lumen interfaces of both the near and far walls (in an area uninvolved by discrete plaque). Gain settings should be optimized to limit 'blossoming' of the brighter interfaces. Following conversion to a full-screen display, M-mode imaging of the distal common carotid artery should be recorded with particular attention to continuous imaging of the lumen-intima interface. Using the cine or freeze-frame function, preliminary measurements of the intimal-medial thickness of the far wall at end-diastole should be made on several cycles (time permitting) and entered onto the Sonographer Worksheet.

The complete protocol is videotaped and the procedure is repeated on the contralateral artery.

Clinical Alerts and Referral Criteria The presence of significant obstruction (>50%) constitutes a clinical alert. Such studies will be identified at the Reading Center and processed within 48 hours of receipt. Results of such studies will be reported by telephone to the Field Center. The presence of ≥75% obstruction should result in immediate referral whereas obstruction of 50-74% should result in routine referral. The detection of non-obstructive plaque (<50%) should provoke assessment of risk factors for atherosclerosis and discussion between the physician and the SHS subject regarding their reduction at the next routine visit.
**TABLE 2: CAROTID IMAGE ANALYSIS PROTOCOL**

**Logsheets:** The sonographer will keep two log sheets, one with the subjects' full name, age, gender, height and weight and the other with the last name and first initial. Other information will include study date, tape number, SHS number and social security number.

**Sonographer Worksheet:** The sonographer will complete a limited worksheet (see page 11) following performance of the study which will include study center, study date, SHS number and social security number. The worksheet will provide information regarding the technical aspects of the study (image quality); plaque presence, location and diameter; and intimal-medial thickness of the far wall.

**Reading Center Equipment:** The Reading Center is equipped with a personal computer into which a frame-grabber has been inserted and connected to a high-resolution video monitor and professional videocassette recorder. Customized software allows acquisition in real time of two-dimensional or M-mode frames thus bypassing image degradation which might occur were analyses to be performed on stop-frame images.

**Review of Videotape:** The videotape of each study will be reviewed in its entirety at the Cornell Reading Center. Whenever a plaque is detected, that frame showing maximum diameter of the plaque (either longitudinal or cross-sectional) will be acquired in real time using the frame grabber and stored on a diskette. Suitable frames including M-mode imaging of the both distal common carotid arteries demonstrating continuous tracing of the lumen-intima interfaces of the near and far walls will be acquired in real-time and stored on diskette. The frame number of each image acquired in this context will be recorded on a worksheet.

**Measurement Techniques:** Measurements will be recorded on an electronic worksheet (see page 12). Plaque will be graded as present/absent, according to side and location, and quantified by maximum diameter (mm), diameter reduction (%; if available, given the plaque location and geometry of the vessel), peak velocity (if diameter reduction is ≥50%) and percent lumen stenosis (<50%, 50-74%, ≥75%). Following calibration for depth, measurement of the intimal-medial thickness of the far wall at end-diastole (minimum diameter) will be made on as many cycles as are available on the acquired frame and averaged. Minimum and maximum diameters will be measured by continuous tracing of the lumen-intima interface of the near and far walls on sequential cycles and averaged.

**Data Summary and Transmission:** Measurements on the worksheet will be verified by an investigator for faithfulness to the analyzed image and for outlier values before being transferred by diskette for incorporation in the main computer database.
## SONOGRAPHER WORKSHEET

| Sonographer: __________________________ | Last name, first initial: __________________________ |
| Study center: ________________________ | SHS number: ________________________________ |
| Study date: ________________________ | Social security number: ________________________ |
| Tape number: ________________________ | Frame numbers: ______________________________ |
| Technical quality: | Left: excellent ___ | good ___ | poor ___ |
| Right: excellent ___ | good ___ | poor ___ |

### Brachial Blood Pressure:

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<th>Plaque Location</th>
<th>+/-</th>
<th>Plaque Diam (mm)</th>
<th>Vessel Diam (mm)</th>
<th>Diameter Reduction (%)</th>
<th>Peak Velocity (m/sec)*</th>
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*Obtain only if diameter reduction ≥ 50%

### M-mode common carotid dimensions

| L CCA far wall, end-diastole |     |     |     | Average |     |
| R CCA far wall, end-diastole |     |     |     |         |     |

### Clinical Alert

Yes _____
**READER WORKSHEET**

Study date
Study center
SHS number
Social security number

**Common carotid dimensions**

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<td>L CCA diameter, minimum</td>
<td></td>
</tr>
<tr>
<td>L CCA diameter, maximum</td>
<td></td>
</tr>
<tr>
<td>R CCA diameter, minimum</td>
<td></td>
</tr>
<tr>
<td>R CCA diameter, maximum</td>
<td></td>
</tr>
</tbody>
</table>

**Plaque Location**

<table>
<thead>
<tr>
<th>Plaque Location</th>
<th>+/- Diam (mm)</th>
<th>Plaque Diam (mm)</th>
<th>Vessel Diam (mm)</th>
<th>Diameter Reduction (%)</th>
<th>Peak Velocity (m/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L CCA, near</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>L CCA, far</td>
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<tr>
<td>L bulb, near</td>
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<tr>
<td>L bulb, far</td>
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<tr>
<td>L ICA, near</td>
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<td></td>
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<tr>
<td>L ICA, far</td>
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<tr>
<td>L ECA, near</td>
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<tr>
<td>L ECA, far</td>
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<td></td>
</tr>
<tr>
<td>R CCA, near</td>
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<tr>
<td>R CCA, far</td>
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<tr>
<td>R bulb, near</td>
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<tr>
<td>R bulb, far</td>
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<tr>
<td>R ICA, near</td>
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<tr>
<td>R ICA, far</td>
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<tr>
<td>R ECA, near</td>
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<td></td>
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<tr>
<td>R ECA, far</td>
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</tbody>
</table>
TABLE 3: PROCEDURE FOR ARTERIAL APLANATION TONOMETRY

1. Subject will remain in the supine position following completion of the carotid ultrasound study. Brachial blood pressure will be determined by the sonographer at this time using a cuff and mercury sphygmomanometer. The first and fifth Korotkoff sounds will be used as systolic and diastolic pressures, based on the average of three sequential determinations.

2. The following information will be typed into the SphygmoCor system: **first screen** (Appendix, page 1): Patient ID=SHS number, family name, first name, sex, date of birth, patient code=social security number; **second screen** (Appendix, page 2): radial artery, systolic blood pressure, diastolic blood pressure, operator ID=employee ID #; other data needn't be included.

3. The applanation tonometer is positioned over the left or right radial artery (whichever is most accessible) and manipulated to obtain an arterial pressure waveform of an appropriate contour with the highest pulse pressure (Appendix, page 3). Following stabilization of the recording, the space bar on the laptop computer will be pressed and a series of waveforms will be acquired for processing. A report is generated automatically and displayed on two computer screens which can be viewed with the space bar (Appendix, page 4).

4. The data acquired will be stored on diskette and sent to the Cornell Reading Center. In addition, a one page print-out (Appendix, page 5) of the data will be generated as back-up and forwarded to Cornell. Following verification of fidelity of the pressure waveform, data will be transferred by diskette for incorporation in the main computer database.

5. Monthly back-up of the SphygmoCor database should be performed as indicated in the SphygmoCor manual (Section 5.2, version 4.0). The diskettes should be forwarded to the Reading Center.
TABLE 4: ARTERIAL WAVEFORM ANALYSIS PROTOCOL

Regional compliance characteristics of the carotid artery will be estimated using methods which incorporate carotid artery imaging and central arterial pressure waveforms back-calculated from the radial artery tonometry by means of validated transfer functions (44,46). These estimates of arterial compliance will be derived from primary measurements stored in the main database:

**Arterial stiffness** (beta), the inverse of compliance, is estimated using the approach of Hayashi et al (57), according to the formula:

\[
\beta = \ln\left(\frac{P_s}{P_d}\right)/\left(\frac{\left[D_s-D_d\right]}{D_d}\right),
\]

where \(P_s\) and \(P_d\) are peak-systolic and end-diastolic pressures, respectively, \(D_s\) and \(D_d\) are peak-systolic and end-diastolic dimensions, respectively. This method has been shown to be independent of changes in distending pressure (58) and to correlate with severity of autopsy-proven severity of atherosclerosis (59).

**Peterson's elastic modulus** \((E_p)\), an estimate of vascular stiffness which does not account for differences in distending pressure (60), is calculated according to the formula:

\[
E_p = \left(\frac{P_s-P_d}{\left[D_s-D_d\right]}\right) \times D_d.
\]

**Young's modulus** \((E)\), which takes into account structural adaptive changes of vessel wall thickness (61), is calculated according to the formula:

\[
E = \left(\frac{P_s-P_d}{\left[D_s-D_d\right]}\right) \times \left(D_d/h\right).
\]

where \(h\) is carotid artery wall thickness (intima plus media).

**Augmentation index**, a quantitative measure of the rapidity of wave reflection, will be measured from the arterial pressure waveform (48) and is automatically generated by the Sphygmocor system.
REFERENCES


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45. O'Rourke MF, Lei J, Gallagher DE, Avolio AP. Determination of the ascending aortic pressure wave augmentation from the radial artery pressure pulse contour in humans.


55. Liu JE, Roman MJ, Spitzer MC, O'Grady MJ, Schwartz JE, Pickering TG, Laragh JH, Devereux RB. Elevated ambulatory with normal clinic blood pressure ("white coat normotension") is associated with cardiac and arterial target organ damage. Am J Hypertens 1995; 8:42A.


First screen: Patient Identification Data

Figure 4.4.1: A sample of the Patient Identification Screen (Patient Screen).
Appendix 2

Second screen: Tonometry Data

![Tonometry Data Screen]

**Figure 4.5.1: A copy of the Tonometry Screen containing typical data.**
Figure 4.6.1: A sample of the Pulse Data Screen
Figure 4.7.1: A sample report, page 1 of 2.

Figure 4.7.2: A sample report, page 2 of 2.
One Page Report (hard-copy)

PATIENT DATA
SMITH, John Michael
Patient ID : 4527
Patient Code : ns
Age 42 (01 Jan 1954), male, 175 cm
Address : 31 Hope Street
Ermington NSW 2115
Medication : nil

STUDY DATA
18 Jun 96, 17:40
Operator ID : ns

radial (199)
aortic

RADIAL PULSE WAVEFORM
AORTIC PULSE WAVEFORM

Blood Pressure
1st Peak
Aug. Index
Maximum dP/dt
125/78 (91) mmHg
26% XED, 83% XED
24% (P2/P1)
654 mmHg/s

Blood Pressure
1st Peak
Aug. Index
Maximum dP/dt
106/79 (91) mmHg
41% XED, 117 ms
24% (P2/P1)
80% XED, 219 ms

CENTRAL HAEMODYNAMIC PARAMETERS

TIMING DATA
Heart Rate, Period
Eject. Duration (ED)
Diast. Duration
SubEnd.Viaab. Ratio
74 bpm, 810 ms
35%, 282 ms
65%, 520 ms
166% (2860/3417)

PRESSURE DATA
Pulse Height (PH)
P1 Height (P1-DP)
Augmentation (AG)
Aug. Index (P2/P1, AG/PH)
Mean Press. (Syst/Diast)
End Systolic Pressure
27 mmHg
27 mmHg
-3 mmHg
85%, -11%
99 / 87 mmHg
96 mmHg

PHU Medical

Figure 4.7.5:
A sample of the Sphygmocor printed report.