# Clinical Utility of an Office-Based Non-Invasive Measure of Arterial Compliance for Predicting Atherosclerotic Burden in Men and Women

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**Introduction**

Office-based risk assessment using the Framingham Coronary Heart Disease Risk Score (FCRS) has been recommended to classify individuals at low, intermediate, and high risk of coronary events([1]). Blood levels of a variety of novel risk factors, including C-reactive protein (CRP), have also been suggested as a potential means to help identify individuals likely to benefit from more aggressive therapy ([2]). In spite of these recommendations, a substantial number of coronary events occur each year in individuals who have not been identified as having coronary artery disease or being at risk of such disease. Obviously, current tools have not allowed physicians in the primary care setting to identify persons who have undetected sub-clinical disease, and methods available for improving our ability to detect such disease are likely to be both invasive and expensive.

Early identification of persons with undetected coronary artery disease or systemic atherosclerotic disease who are at risk of coronary events can reduce the risk of these events. Results from the AFCAPS/TexCAPS study ([3]) and the Heart Protection Study ([4]) indicate statin therapy is effective in patients with sub-clinical disease. However, indiscriminate use of statin therapy and other forms of pharmacologic intervention in all low risk subjects would be prohibitively expensive and subject large numbers of individuals to unnecessary side effects. Thus, more effective strategies are required to direct drug therapy for non-ATPIII drug therapy eligible individuals who may nevertheless benefit from more aggressive treatment. To be successful, such strategies need to be easily accessible to large numbers of primary-care physicians where screening for, and initiation of, primary prevention efforts would be most effectively implemented.

**[J. Raines needs to add sentences about why atherosclerotic burden is a good surrogate for risk of coronary events and why abdominal aorta is a good measure of atherosclerotic burden]**

Recently, measurement of arterial stiffness has emerged as a simple noninvasive means to identify subjects with sub-clinical systemic atherosclerosis. Recognition and early treatment of increased aortic and proximal arterial stiffness is also important because of their role in the development of isolated systolic hypertension, left ventricular hypertrophy, and congestive heart failure.

The purpose of the current study was to examine the association between measures of arterial compliance, using an automated, non-invasive air plethysmographic technique with extent and severity of atherosclerosis, as measured by magnetic resonance imaging of the abdominal aorta and to evaluate the predictive value of arterial compliance independent of conventional and novel risk factors.

## METHODS

### Study Population

During the period October 2001 through June 2002, researchers conducted two studies to characterize the performance of an automated, non-invasive air plethysmographic device designed to measure systemic atherosclerosis (Vasogram ™). The first study (Study 1) was conducted at seven institutions (Atlanta Veterans Administration Hospital, Baylor University Medical Center, Columbia University Medical Center, Jackson Hospital at the University of Miami Medical Center, the Medical University of South Carolina, Wake Forest University Medical Center, and a private clinical center in Asheville, NC) with approval of the institutional IRBs at each site. This study was conducted on 465 male and female subjects with no history of cardiovascular disease. This population was used to characterize Vasogram precision and to characterize the distribution of Vasogram measurements in a population with no documented cardiovascular disease. The study was designed to enroll at least 420 subjects (35 in each of 12 groups defined by gender six 10-year age intervals over the ages 21 through 80). The second study (Study 2) was conducted at four institutions (Atlanta Veterans Administration Hospital, Columbia University Medical Center, Jackson Hospital at the University of Miami Medical Center, and Wake Forest University Medical Center) with approval of the institutional IRBs at each site. This study was designed to enroll at least 320 subjects (40 males and 40 females in each of four cardiovascular risk groups). The actual enrollment was a total of 343 subjects.

Because one objective of Study 1 was to characterize the distribution of Vasogram measures in persons with no evidence of cardiovascular disease, the study enrolled ambulatory males and non-pregnant females between 21 and 80 years of age that met the following criteria: nonsmokers (no tobacco consumption over last 5 years; normotensive (include absence of antihypertensive medication usage; nondiabetic; normal blood lipids (LDL < 160 mg/dl, HDL > 35 mg/dl, and triglycerides < 300 mg/dl); body mass index less than 40 $kg/m^2$; and no history of cardiovascular disease. Study 2 enrolled subjects with a range of cardiovascular risk as defined by the following four risk categories. Risk Group 1 comprised healthy subjects who were free of cardiovascular disease with a body mass index (BMI) < 40 $kg/m^2$ and a 10-year risk for a future CHD event of <10% based on the Framingham Risk Score. Subjects were classified as being free of cardiovascular disease if they had no history of coronary heart disease and a normal resting electrocardiogram (ECG), a negative Rose Angina Questionnaire, and an ankle/brachial index >0.90. Risk Group 2 was defined as subjects free of cardiovascular disease but with a Framingham 10-year risk for CHD of between 10% and 20%. Risk Group 3, the CHD equivalent group, included individuals free of cardiovascular disease but with a Framingham CHD 10-year risk of greater than 20%, diabetes, an ankle /brachial index < 0.90, or evidence of cerebrovascular disease. Risk Group 4 included subjects with coronary artery disease documented by cardiac catheterization (at least one lesion >50% stenosis) in a major epicardial coronary artery, a prior Q-wave myocardial infarction, or history of coronary revascularization. The age range for subjects in all risk groups was 35 to 69 years for males and 45 to 79 years for females. Subjects were excluded from the study if they had active infections (excluding skin infections); if they were taking antibiotics, immunosuppressive drugs, or steroids; or if the site Principal Investigator considered them to be inappropriate for the study.

**Study Measurements**

Study 1 focused on characterizing and optimizing the performance of the Vasogram™. It involved only two replicated measurements of thigh and calf peripheral arterial compliance taken within a short period of time (typically about 10 minutes).

Study 2 involved 4 repeated measurements of thigh and calf arterial compliance on subjects classified within the 4 cardiovascular disease risk groups defined above, as well as other measures of cardiovascular risk. Two of the repeated Thigh and Calf MaxV50 measurements were taken on two separate days, and the 3rd and 4th measurements were taken on a 3rd day. Other measures of cardiovascular risk included a battery of blood chemistries (e.g. full lipid profile, C-reactive protein), stress electrocardiogram, and all measures needed to compute a Framingham coronary risk profile. As described in the subsections below, MRI measurements were taken from the abdominal, descending, and ascending aortas to obtain a measure of atherosclerotic burden, while the Vasogram measures were combined to create an overall measure of peripheral arterial compliance that can be used as a screen for atherosclerotic burden.

**Computation of a Single Peripheral Arterial Compliance Measure**

*Description of the Vasogram as a Measure of Arterial Compliance*

In both studies, measurements of peripheral arterial compliance were taken in the thigh and calf, called Thigh and Calf MaxV50. Arterial compliance was measured with a fully automated computer- controlled air plethysmograph designed for clinical use (Vasogram ™). The device consists of an air pump, calibration chamber, and high-resolution pressure transducer (Fig. 1). The interface with the patient is via standard blood pressure cuffs. The cuffs are placed at the Thigh and Calf and measurements at these levels are taken independently. Cuff pressures were inflated to 30 mmHg below diastolic pressure, and segmental limb volume change as a function of time during the cardiac cycle was recorded (Fig. 2). The cuff pressure was then increased in 10 mmHg increments and the process repeated until the peak cardiac cycle dependent volume change was reached (Fig. 3). At each cuff pressure, during early diastole, a calibration volume of 0.65 mL was rapidly introduced to calibrate the system. To determine the local arterial compliance, the maximum volume change (MaxV) was divided by the subject's brachial pulse pressure. This value was normalized to a 50mmHg pulse pressure (MaxV50) to facilitate comparison among patients. Higher scores for MaxV50 correspond to more compliant arteries.

*Combined MaxV50 Score Calculation*

To facilitate the clinical utility of the Vasogram as a screening tool, the data from Study 1, which had possibly 2 repeated Vasogram measurements per subject available for analysis, and Study 2, which had possibly 4 repeated Vasogram measurements per subject available for analysis, were used to develop a single peripheral arterial compliance measure called a "Combined MaxV50 Score." This score combines information from the Thigh MaxV50 and Calf MaxV50. This combined measure was then evaluated using only data from Study 2. The Combined MaxV50 Score is scaled to a Thigh MaxV50 measurement by averaging a Thigh MaxV50 estimate and a Calf MaxV50 estimate normalized to the scale of a Thigh MaxV50 measurement. One additional benefit of the algorithm used to calculate the Combined MaxV50 Score is that it provides a quality control measure in addition to providing a single measure of peripheral arterial compliance.

The procedure for computing the Combined MaxV50 Score is based on the underlying assumption that systemic atherosclerosis should be reflected in both the thigh and calf measurements. Consequently, the procedure relies on first evaluating the agreement of the thigh and calf measurements, as a quality control check, and then averaging measures that "agree." The computational procedure is outlined conceptually in Figure 4 and described in detail in the paragraphs below.

Computationally, a Combined MaxV50 Score is calculated by first transforming the Thigh and Calf MaxV50 measurements into percentiles based on the analysis of the healthy subject sample collected in Study 1. If the absolute difference in the Thigh and Calf MaxV50 percentiles is 0.2 or less, these two values are used to obtain the combined score. The Calf MaxV50 measurement is normalized to the scale of a Thigh MaxV50 measurement and the Thigh MaxV50 and the transformed Calf MaxV50 are averaged to obtain the Combined Max V50 Score. The normalizing function is based on a simple linear regression analysis of the Calf MaxV50 and Thigh MaxV50 measurements taken in Study 1 and Study 2.

If the Thigh and Calf MaxV50 percentiles differ by more than 0.2, a second measure is necessary. The second measure is taken to try and determine whether or not the calf and thigh arterial compliance disagreement is due to a faulty test or subject physiology. If Thigh and Calf MaxV50 percentiles differ by more than 0.2 on the second test and two thigh percentiles do not differ by more than 0.2 and the two calf percentiles do not differ by more than 0.2, then the test is assumed to be good and the subject has a physiological reason for the calf / thigh disagreement.

If a subject has physiological calf/thigh disagreement, then a Combined MaxV50 Score is not calculated. The two measures are summarized under the assumption that the physiological calf/thigh disagreement is clinically relevant, and reporting a Combined MaxV50 Score is deemed inappropriate. If the second Thigh and Calf MaxV50 measurements do not differ by more than 0.2 and either the two Thigh MaxV50 measurements or the two Calf MaxV50 measurements do not differ by more than 0.2, then the first Calf MaxV50 or Thigh MaxV50 measure that disagrees with the remaining tests is assumed to be a faulty test. If the second Thigh and Calf MaxV50 measurements do not differ by more than 0.2 and the two Thigh MaxV50 measurements do not differ by more than 0.2, then the second Calf MaxV50 measurement is transformed into a value that is on the scale of a Thigh MaxV50 and the two Thigh MaxV50 measurements are averaged and finally the transformed Calf MaxV50 and the average Thigh MaxV50 values are averaged to calculate the Combined MaxV50 Score. If the second Thigh and Calf MaxV50 measurements do not differ by more than 0.2 and the two Calf MaxV50 measurements do not differ by more than 0.2, then the two Calf MaxV50 measurements are averaged and the average is transformed into a value that is on the scale of a Thigh MaxV50 and finally the transformed Calf MaxV50 average and the second Thigh MaxV50 values are averaged to calculate the Combined MaxV50 Score.

*Defining an Abnormal Vasogram Score*

Using the data from Study 1, the Combined MaxV50 Score was calculated for the total of 316 subjects who had valid data available for the calf and thigh measurements and who did not have calf/thigh disagreement. Based on these scores, screening cut points for the Combined Max V50 were generated for specific categories defined by gender and age group. For purposes of the analyses presented in this paper, two cut points were considered, one at the 25$^{th}$ percentile

and one at the 50th percentile. Using these criteria, a person is said to "fail" the screening test in the sense that they are deemed to be at high risk of atherosclerosis if they fall below the 25th percentile of the healthy normal population (or alternatively the 50th percentile for the second cut point.

**Determination of Atherosclerotic Burden by MRI**

In Study 2, images of the wall of the abdominal aorta were acquired with fast-spin echo double inversion recovery techniques used previously to characterize the wall of the thoracic aorta [redacted]. All scans were performed in each subject by highly experienced research magnetic resonance imaging technologists under supervision of a trained cardiologist or radiologist. Images were obtained using 1.5 Tesla full body imaging systems (two GEMS, one Picker, and one Philips) with torso array coils wrapped around the abdomen. Axial images of the abdominal aorta were acquired from the renal arteries to the aortic bifurcation in one-centimeter increments (5mm thick slice with 5 mm gap). Both T2 and proton-density weighted images were acquired according to previously published techniques with ECG gating and respiratory compensation incorporating a 20 centimeter field of view and a 256 x 256 acquisition matrix with no phase wrap ([5,6]). Other imaging parameters included: TR = 2 RR intervals, TE = 12 ms (PDW) and TE = 60 ms (T2W), 2 NEX, 32 to 64 Echo-train length, +64-kHz receiver bandwidth, and chemical shift suppression.

Upon acquisition, images were archived in DICOM II format and transferred to the core imaging reading center by FTP Transfer or optical disk. Using software approved for beta testing by the FDA, ([7,8])the lumen and outer wall boundary of the abdominal aorta were identified in each slice on both the T2 and PDW image ([9]). The T2 or PDW image with the clearest delineation of the boundaries of interest was used in subsequent analyses. This technique has been shown most accurate in identifying the true wall boundary when compared to ex vivo and in vivo plaque morphology ([9]).

After determining the lumen area and total vessel area within the external wall boundary, Wall Area was defined as the difference between total vessel area and lumen area. Percent Wall Area was defined as the ratio of Wall Area to total area (%Wall Area= 100 * Wall Area/Total vessel area). The Mean %Wall Area was defined as the mean of the slice-specific %Wall Area across all slices of the abdominal aorta (Fig.2). The operational definition of atherosclerotic disease for this manuscript was defined as the highest quartile of Mean %Wall Area averaged across Risk Groups 1 through 3.

**Statistical Analysis**

The primary objective of the statistical analyses reported here is to establish the sensitivity and specificity of the Vasogram™ as a screening tool for atherosclerotic burden measured in the abdominal aorta. For Study 2, a total of 178 subjects (88 males and 90 females) in Risk Groups 1 through 3 (Subjects in Risk Group 4 with known cardiovascular disease were excluded from these analyses) had sufficient data to be classified as positive (high risk for atherosclerotic disease) or negative on the Vasogram screening test and diseased or non-diseased based on the MRI outcome measures. Standard contingency table procedures were used to characterize the sensitivity and specificity of the test using the two cut points defined above, and large sample binomial procedures were used to generate 95% confidence intervals for these

estimates. As a point of comparison, the sensitivity and specificity were also computed for the Framingham Risk Profile. In using the Framingham Risk Profile as the predictor, subjects in Risk Group 3 were defined as at high risk of systemic atherosclerosis while those in Risk Groups 1 and 2 were considered not at high risk.

## RESULTS

Table 1 summarizes the characteristics of the Study 2 subjects that were used to generate the Vasogram™. From Study 2, 86 males and 91 females in Risk Groups 1 thorough 3 had sufficient Vasogram and MRI data to allow calculation of sensitivity and specificity. Table 1 describes how these subjects were derived from the original study subjects and presents demographic information on the subjects.

Using the 25$^{th}$ percentile as a cut point for defining a positive test, the sensitivity of the Vasogram for females was 0.77 with a 95% CI of (0.59, 0.95), while the specificity was 0.72 with a 95% CI of (0.61, 0.83). Similarly, with the 25$^{th}$ percentile as a cut point for defining a positive test, the sensitivity of the Vasogram for males was 0.60 with a 95% CI of (0.35, 0.85), while the specificity was 0.73 with a 95% CI of (0.63, 0.83). Using the 50$^{th}$ percentile as a cut point for defining a positive test, the sensitivity of the Vasogram for females was 0.86 with a 95% CI of (0.72, 0.99), while the specificity was 0.49 with a 95% CI of (0.37, 0.61). Similarly, with the 50$^{th}$ percentile as a cut point for defining a positive test, the sensitivity of the Vasogram for males was 0.73 with a 95% CI of (0.51, 0.95), while the specificity was 0.47 with a 95% CI of (0.36, 0.58).

Another Characteristic of interest is the positive and negative predictive value of the Vasogram test as it might be used in the clinical site. While sensitivity and specificity are properties of the diagnostic test, positive and negative predictive value depend not only on the sensitivity and specificity of the test, but also on the prevalence of disease in the population being tested. Table 3 summarizes the positive and negative predictive value of the Vasogram™ for disease prevalence ranging from 5% to 50%. As show in the table, the Vasogram™ results in about a 50% improvement in identifying underlying disease in populations with this range of disease.

For comparison, note that using the standard risk factors as a comparison, the sensitivity for females was 0.70 with a 95% confidence interval of (0.50, 0.90), while the specificity was 0.73 with a 95% confidence interval of (0.63, 0.83). Similarly, the sensitivity for females was 0.40 with a 95% confidence interval of (0.19, 0.61), while the specificity was 0.44 with a 95% confidence interval of (0.34, 0.54). Of the 22 females and 15 males in Risk Groups 1 through 3 defined by MRI as having atherosclerotic disease, none were identified as high risk by ECHO.

## DISCUSSION

**Topics for Discussion per meeting at Rho**

- **Limitations**
    - **Can't address all patients**

- **Lack of independent assessments of how much burden constitutes disease with some discussion about how we tried to address this limitation.**
- **Used our Study 2 to define cut points with no second population to validate**

- **Issues of CPT and reimbursement**
- **Simplicity of test**

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Table 1. Characteristics of Study 1 Population

| | | |
|---|---|---|
| Total Subjects | | 465 |
| Mean Calf MaxV50 | | 417 |
| Mean Thigh MaxV50 | | 413 |
| Mean Combined MaxV50 | | 301 |
| Gender, N (%) | | |
| | Male | 169 (56%) |
| | Female | 132 (44%) |
| Age, mean (range) | | 48.83 (21 – 78) |
| | Male | 48.48 (21 – 77) |
| | Female | 49.10 (21 – 78) |
| Mean Calf MaxV50, mean (SD) | | 1.87 (0.65) |
| | Male | 2.22 (0.62) |
| | Female | 1.60 (0.53) |
| Mean Thigh MaxV50, mean (SD) | | 4.16 (1.41) |
| | Male | 4.90 (1.44) |
| | Female | 3.58 (1.09) |
| Mean Combined MaxV50, mean (SD) | | 4.10 (1.35) |
| | Male | 4.87 (1.32) |
| | Female | 3.50 (1.02) |

Table 2. Characteristics of Study 2 Population

| | | |
|---|---|---|
| Total Subjects | | 343 |
| Mean Calf MaxV50 | | 342 |
| Mean Thigh MaxV50 | | 341 |
| Mean Combined MaxV50 | | 284 |
| Abdominal Aorta %Wall Area From Good Quality MRI | | 268 |
| Good Quality Abdominal %Wall Area and Mean Combined MaxV50 | | 223 |
| Good Quality Abdominal %Wall Area and Mean Combined MaxV50 in Risk Groups 1-3 Only* | | 178 |
| Gender, N (%) | | |
| | Male | 88 (49%) |
| | Female | 90 (51%) |
| Risk Group, N (%) | | |
| | 1 | 66 (30%) (31M, 35F) |
| | 2 | 54 (24%) (27M, 27F) |
| | 3 | 58 (26%) (30M, 28F) |
| Age, mean (range) | | 56.76 (35 – 79) |
| | Male | 54.22 (35 – 69) |
| | Female | 59.26 (46 – 79) |
| Mean Calf MaxV50, mean (SD) | | 1.82 (0.75) |
| | Male | 2.18 (0.77) |
| | Female | 1.47 (0.53) |
| Mean Thigh MaxV50, mean (SD) | | 3.84 (1.49) |
| | Male | 4.65 (1.47) |
| | Female | 3.05 (1.00) |
| Mean Combined MaxV50, mean (SD) | | 3.92 (1.53) |
| | Male | 4.73 (1.53) |
| | Female | 3.14 (1.04) |
| % Wall Area, mean (SD) | | 42.09 (6.45) |
| | Male | 39.86 (5.50) |
| | Female | 44.25 (6.59) |

* Summary Statistics are based on the subjects in risk groups 1-3 with good quality abdominal %wall area measurements and a mean Combined MaxV50.

Table 3. Estimates of Positive and Negative Predictive Value

| Underlying Prevalence of Disease | Estimates of Predictive Value | | | |
|---|---|---|---|---|
| | Females, Se=0.77, Sp=0.72 | | Males, Se=0.60, Sp=0.73 | |
| | Positive Predictive Value | Negative Predictive Value | Positive Predictive Value | Negative Predictive Value |
| 0.05 | 0.13 | 0.98 | 0.10 | 0.97 |
| 0.10 | 0.23 | 0.97 | 0.20 | 0.94 |
| 0.15 | 0.33 | 0.95 | 0.28 | 0.91 |
| 0.20 | 0.41 | 0.93 | 0.36 | 0.88 |
| 0.25 | 0.48 | 0.90 | 0.43 | 0.85 |
| 0.30 | 0.54 | 0.88 | 0.49 | 0.81 |
| 0.35 | 0.60 | 0.85 | 0.54 | 0.77 |
| 0.40 | 0.65 | 0.82 | 0.60 | 0.73 |
| 0.45 | 0.69 | 0.79 | 0.65 | 0.69 |
| 0.50 | 0.73 | 0.76 | 0.69 | 0.65 |