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Non-Invasive Detection of Vascular Disease in the Arteries of the Lower Extremity; Clinical Evaluation of QuantaFlo™ Compared to Doppler and Definitive Imaging

Authors:
Matthew E. Schaefer, DO; San Antonio Kidney Disease Access Center, 7114 San Pedro Ave., San Antonio, TX 78216; mschaefer@sakdc.com
John B. Long, MD; Vascular Specialists of San Francisco, 3838 California St., Suite 612, San Francisco, CA 94118; drjlong@aol.com
Charles Pollick, MD; Los Angeles Cardiology Associates, 1245 Wilshire Blvd, Los Angeles, CA 90017; pollick@lacard.com

Abstract:
Objective: Peripheral artery disease (PAD) affects 8 – 18 million Americans. Under-diagnosis of the disease remains a clinical dilemma. Doppler ankle-brachial index (ABI) with pressure cuffs is the most common initial test performed when suspecting PAD. Since 2011, vascular specialists and primary care physicians have used a PAD testing device such as the FloChec® System and more recently the QuantaFlo™ System, a blood volume wave form visualization and evaluation tool, in their evaluation of lower extremity PAD. This study compared the accuracy of the QuantaFlo™ System to ABI, using primarily duplex ultrasound (Duplex) to confirm the presence or absence of PAD.

Methods: The PAD testing device, Doppler ABI, and Duplex/Angiogram test data were prospectively collected under an Institutional Review Board (IRB)-approved, multi-center, single-arm, post-market study. Test results for each limb and each technology were analyzed and compared by an imaging core lab. The core lab assigned a severity score to each limb upon interpretation. These data were used to design the QuantaFlo™ algorithm to optimize accuracy using a cross-validation trial methodology. QuantaFlo™ was then prospectively validated in a second subject cohort.
Results: A total of 360 limbs from 180 patients were evaluable with PAD testing results, ABI and definitive imaging in the first cohort. Cross-validation trial methodology used test data from 80% of these limbs selected by a random process applied 100 times to create 100 different algorithms. Each algorithm was in turn evaluated on the entire 360 limb database. Mean values from the 100 trials achieved an accuracy of 83.6%, sensitivity of 81.3% and a specificity of 90.0% to detect flow obstruction. Corresponding Doppler ABI results on 360 limbs were 75.6% accuracy, 60.6% sensitivity and 92.8% specificity. Then, the best performing algorithm was incorporated into QuantaFlo™ and a prospective clinical validation on 30 additional limbs from 15 patients demonstrated an accuracy of 89.7%, sensitivity of 89.5% and a specificity of 90.0%.

Conclusion: The QuantaFlo™ method can detect PAD with greater accuracy and sensitivity than Doppler ABI, and can provide a disease severity interpretation. These results suggest clinical utility of QuantaFlo™ in the diagnosis of PAD in the primary care setting.

Key Words
Peripheral artery disease, disease diagnosis, ankle brachial index testing, duplex ultrasound, sensitivity and specificity

Introduction
Peripheral artery disease (PAD) affects 8 – 18 million Americans with an estimated healthcare cost of $290 billion per year [1, 2, 3]. More than half of patients with a diagnosis of PAD also have cardiovascular disease involving the coronary, carotid and aortic arteries [2], and patients with PAD have a 21% combined incidence of death, stroke, myocardial infarction, or death within 1 year [4]. Clinical manifestations range from the 75% of PAD patients who are asymptomatic [5], to the 2 million people affected with Critical Limb Ischemia. Thus identification of PAD is critical to prevent or delay morbidity and mortality in these patients.

Despite the prevalence and severity of PAD, under-diagnosis of the disease remains a problem in the primary care setting [6]. Doppler ankle-brachial index with pressure cuffs (ABI), is the most common initial test performed when PAD is suspected. However, ABI has proven impractical in the primary care setting due to the need for technical expertise, accurate cuff placement and time required to perform the study [7, 9]. As such, many physicians rely upon physical examination, patient history, and risk factor identification to diagnose PAD and then make referrals to vascular laboratories. However, absence of distal pulses alone has a low sensitivity for detection of PAD [9] and approximately 55% of patients referred to a vascular laboratory for ABI are found to not have PAD [8]. These findings highlight the need for a simple, effective screening method for PAD.

A digital volume plethysmography system that produces a blood volume waveform from the posterior tibial and anterior tibial arterial distributions has been used by vascular specialists and primary care physicians since 2011 in their evaluation of lower extremity PAD. A proprietary algorithm calculates a digital ABI, which is analyzed by the physician in order to detect lower extremity flow obstruction.

The data collected in this study was used to develop the QuantaFlo™ System, which is the next generation of PAD testing. A clinical validation was performed to confirm the
presence or absence and the severity of PAD using this enhanced system. The objective of this study was to compare the accuracy of the QuantaFlo™ results to ABI testing, using Duplex/Angiogram to determine the presence or absence of flow obstruction and disease severity in the lower extremities to support the diagnosis of PAD.

**Methods**

From November 2013 through February 2015, five mixed primary and vascular community-based practices enrolled subjects in a single-arm prospective, post-market study. Two new practices replaced two of the original five practices, and from May 2015 through June 2015, these five mixed primary and vascular community-based practices enrolled additional patients in the study. The study was approved by the New England Institutional Review Board. Subjects were prospectively and consecutively evaluated for the study, and each provided voluntary consent for testing and prospective data collection. Subjects self-completed a 12-question PAD questionnaire that identified risk factors and signs and symptoms. At least one question had to be answered ‘Yes’ for inclusion into the study. Subjects without a viable digit (e.g. toe) or who had cardiac or vascular intervention within 30 days were excluded from the study. Enrolled subjects were tested bilaterally with the PAD test device, ABI, and Duplex ultrasound or angiography. All tests were completed within 30 days of office visit. The PAD tests were completed by medical assistants or technicians trained on the technology and the ABI tests were performed by registered vascular technologists.

A vascular core laboratory graded each limb as negative or positive for flow obstruction (OBS) and disease severity using the definitive imaging of Duplex/Angiogram. The reviewer was blinded to the results of the tests at the time of grading. The reviewer was an interventional physician with Registered Physician Vascular Interpreter (RPVI) credentials to read both studies.

**PAD Testing Measurements**

Measurements were performed bilaterally on the lower then upper extremities by placing a sensor on a single digit of each extremity in sequential fashion. During each 15-second measurement, the sensor detects reflected infrared light, which measures the blood volume changes in the brachial, anterior tibial, and posterior tibial arterial distributions. The resulting waveforms were then analyzed by a specially-designed, proprietary algorithm which aggregates and calculates the measurements from the lower versus upper extremities and reports an indexed score for each leg. A PAD testing result of <0.90 was considered positive for OBS.

**Doppler ABI with Pressure Cuff Measurements**

Systolic pressure at one or both arms was measured, along with systolic pressures bilaterally for both the dorsalis pedis and posterior tibial arteries. ABIs were calculated as the maximum ankle pressure divided by the maximum brachial pressure. An ABI of <0.90 was graded as positive for OBS, while an ABI between 0.90 and 1.4 was graded as normal. Incompressible arteries were defined as ABI > 1.4, and were considered negative for OBS in the primary analysis.

**Flow Obstruction by Duplex Scan**

Flow obstruction was diagnosed when any of the following conditions were present on Duplex scans:

- Monophasic waveform that remains reduced distally.
• Peak Systolic Velocity Ratio (PSVR) > 2.0 and reduced waveforms in native vessels, Peak Systolic Velocity (PSV) > 180cm/sec or < 40cm/sec in bypass grafts, PSVR ≥ 2.5 intra-stent, or monophasic waveform with PSV < 50cm/sec in stented tibial arteries.

• 50% or greater focal stenosis in any vessel segment or 40% or greater stenosis if diffuse disease (multi-level disease).

**Flow Obstruction by Angiogram**
In cases in which contrast angiography was performed instead of Duplex, the following criterion was used to diagnose OBS:

• 50% or greater focal stenosis in any vessel segment; or 40% or greater stenosis if diffuse disease (multi-level disease).

**QuantaFlo™ Development**
The collected data was used to develop and validate the QuantaFlo™ System. One hundred algorithms were created to maximize results in each of 100 randomized data groups consisting of 80% of the limbs. No two groups or algorithms were the same. Each algorithm was applied to the entire cohort of limbs and the results recorded for sensitivity, specificity and accuracy. A cross-validation trial methodology was used to verify the results for each set of parameters. A testing result of <0.90 was considered positive for OBS.

The resulting QuantaFlo™ was validated in a clinical study with a separate set of subjects, enrolled in the same manner as the original patient cohort. QuantaFlo™, ABI and Duplex/Angiogram were performed and analyzed in this cohort of subjects as described above.

**Statistical Techniques**
Categorical variables are summarized as proportions or percentages, and corresponding 95% confidence interval (CI) using the Wilson score interval.

Clinical contingency results for each limb and each technology were categorized as: true positive, true negative, false positive and false negative using the definition of OBS. Sensitivity, specificity, and accuracy were calculated using standard methods.

Generalized estimating equations were utilized to calculate the difference in proportions and corresponding confidence intervals for sensitivity, specificity, and accuracy, based upon least squares means for paired binary data. The difference in means, reported as q_{PAD testing} – ABI, where a positive difference indicates greater performance of PAD testing results, and 95% confidence intervals are presented.

Statistical analyses were conducted in SAS version 9.3 (SAS Institute, Cary, N.C.), and graphics were produced with Microsoft® Excel® 2007.

**Results**

**Initial Cohort**
A total of 360 limbs from 180 subjects had results from PAD testing, ABI and definitive imaging tests. Duplex scan was performed with the majority of subjects, with angiogram performed in 18 limbs (10 subjects). All subjects had at least one risk factor for PAD, including hypertension, hyperlipidemia, diabetes mellitus or smoking history.

Figures 1 and 2 summarize the comparative results for PAD testing, QuantaFlo™ and ABI.

The cross-validation trial methodology testing 100 algorithms using the test data from the 360 limbs achieved a mean accuracy of...
83.6%, mean sensitivity of 81.3% and mean specificity of 86.2% to detect flow obstruction. Compared with ABI, PAD Testing mean performance exhibited significantly higher sensitivity, 81.3% (95% CI: 75.0, 86.4) vs. 60.6% (95% CI: 53.3, 67.5) for detecting OBS, similar specificity, 86.2% (95% CI: 79.8, 90.0) vs. 92.8% (95% CI 87.5, 96.1) to predict non-OBS, and significantly higher test accuracy despite slightly overlapping confidence intervals, 83.6% (95% CI: 79.3, 87.2) vs. 75.6% (95% CI: 70.7, 79.8) with reference to the definitive imaging comparator.

The best performing algorithm was incorporated into QuantaFlo™ and subsequently clinically validated in a study of 30 limbs (15 subjects). In contrast to the original study cohort of 360 limbs, the 30 limbs had more calcified and distal extremity disease. QuantaFlo™ had an accuracy of 89.7% (95% CI: 71.5, 97.3), sensitivity of 89.5% (95% CI: 65.5, 98.2) and a specificity of 90.0% (95% CI: 54.1, 99.5). Corresponding Doppler ABI results were 62.1% accuracy, 47.4% sensitivity and 90.0% specificity.
**Discussion**

This study compared relative accuracy, sensitivity and specificity of a digital volume plethysmography based ABI system to a Doppler, blood pressure cuff ABI. Accuracy of a noninvasive vascular test is best determined by comparing it to a ‘gold standard test. In this study Duplex scans and angiography were used. In the first cohort, the raw data collected with the PAD testing device were utilized to develop an enhanced system, QuantaFlo™. Using cross validation methodology, 100 separate algorithms were generated, each from a random selection of 80% of the raw data in the first cohort. 100 trials on the entire set of raw data from first cohort solved for sensitivity, specificity and accuracy of each algorithm. The mean results from 100 trials of 100 algorithms showed that the mean accuracy of the PAD testing system is significantly more accurate than ABI in detecting OBS in lower extremities with statistically higher mean sensitivity than ABI test and comparable specificity. The second cohort prospectively studied the best performing of the algorithms, which is incorporated into QuantaFlo™. This validation study in a cohort of 30 limbs found higher accuracy and sensitivity with similar specificity with this system compared to use of ABI.

This study had a mixed investigator group that included primary care and vascular specialty physicians. This was to assess the device’s performance in a varied diseased population (asymptomatic and symptomatic), where the vascular specialties enrolled a higher diseased population than the primary care physician groups. The results from this study suggest that QuantaFlo™ may be used successfully in either setting as an evaluation tool for diagnosis of PAD.

Non-invasive physiologic testing, such as performance of ABI, is one of the considerations employed by a physician to assess a patient for peripheral arterial disease along with physical examination and patient medical history of cardiovascular risk factors and symptoms. All of the Doppler-based and Duplex tests of this study were performed by trained and certified vascular technologists, while the QuantaFlo™ PAD tests were completed in physician offices by medical assistants or certified medical technicians. In the primary care practice, it is usually not practical to have a trained vascular technologist on staff to perform ABIs. Nicolai et al. [7] noted that operation by non-vascular technologists results in a degradation in the accuracy of the ABI test. Conversely, the QuantaFlo™ PAD testing method may be accurately used by an office staff member with minimal training [10]. The system is completely automated and less subject to technique, settings, or manual calculations. Considering the reduced skill requirements, reliable ease of use, and minimal time required, the QuantaFlo™ PAD testing method may be well suited for the primary care office as well as the vascular specialty office than the ABI method for identifying patients at risk for PAD.

It is expected that some patients will have calcified arteries which are incompressible by blood pressure cuff techniques [11] especially in the elderly or diabetic patients. When this condition occurs in the legs, the ABI testing method might give non-physiologic measurements (>1.4). Vascular specialists consider such results to be indeterminate or inconclusive. The QuantaFlo™ System does not use a pressure cuff so it is able to acquire physiologic measurements of incompressible arteries.
In the second validation cohort, there was a higher frequency of calcified arteries and distal lower extremity disease than in the first cohort, which may explain the lower than usual performance of ABI in the second cohort [12].

**Study Limitations**
The study enrolled a relatively small patient cohort without strict inclusion and exclusion screening criteria, and data regarding patient recruitment with respect to the number of consecutive patients not enrolled were not formally tracked. A larger cohort size may uncover clinically significant differences in accuracy or sensitivity or specificity, and allow for different population subgroup analyses to further assess clinical utility. The study was acute in nature without serial follow-up to assess any changes to the test findings over time. Additionally, the participating clinical sites were mixed physician practices enrolling a more diseased population that may not be representative of the general population, as in terms of percentage of limbs with flow obstruction (OBS).

Having all patients undergo contrast angiography would be more definitive than the current study which relied predominately on Duplex results as detection for PAD. Duplex scans have been reported to be unreliable to visualize arteries adequately in 20% of cases, predominantly below the knee [13, 14]. However, it was not deemed ethically appropriate unless clinically indicated and medically necessary for patients to have an invasive diagnostic procedure such as contrast angiography.

**Conclusions**
The PAD testing method (QuantaFlo™) can reliably detect flow obstruction to support PAD diagnosis, with higher accuracy, higher sensitivity and similar specificity compared to ABI. QuantaFlo™ can be performed in a convenient fashion in the primary care office without requiring complex equipment and highly trained personnel. QuantaFlo™'s higher accuracy and sensitivity may facilitate patient identification for peripheral vascular disease when used adjunctively with physical examination and patient medical history.
Abbreviations
(PAD): Peripheral Artery Disease; (ABI): Ankle-Brachial Index; (dABI): digital Ankle-Brachial Index; (CVD): Cardiovascular Disease; (OBS): Flow Obstruction; (RPVI): Registered Physician Vascular Interpreter; (PSVR): Peak Systolic Velocity Ratio; (CI): Confidence Interval; (n): Number Of Observations; (N): Number with Evaluable Data; (ROC): Receiver Operating Characteristic; (AUC): Area Under The Curve.

Competing Interests
Dr. Schaefer was compensated to serve as vascular core laboratory for this study.

Authors' Contributions
MS, JL and CP conceived the idea for the manuscript. MS analyzed the data and drafted the paper. JL and CP contributed additional review commentary.

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