Approximately 10.9 million Americans have been physician-diagnosed with diabetes, an estimated additional 5.7 million people remain undiagnosed, and an additional 14.2 million people are in a pre-diabetic state. Cardiovascular disease remains the primary cause of diabetes-associated morbidity and mortality. Two-thirds of people with diabetes die of heart or vascular disease. The impact of diabetes on cardiovascular disease is further illustrated by the fact that the risk of developing a myocardial infarction (MI) in diabetic patients without known heart disease is equivalent to the risk observed in non-diabetic survivors of a prior infarction. Results of the CUPS trial suggest that many patients with diabetes already have evidence of early stage cardiovascular disease and it is essential that these patients be treated early with proven therapies to reduce their risk of future cardiovascular events. The CHECKMATE trial evaluated 30-day clinical outcomes after initial presentation of cardiovascular disease symptoms in both a diabetic and non-diabetic population. The results substantiate the need for early detection of cardiovascular disease within the diabetic population as the overall major acute coronary event (Death/MI/Revascularization) rate was 3-fold higher in the diabetic cohort (19% to 6%, respectively). Estimates from the World Health Organization suggest that the total number of diabetic patients will more than double by the year 2025. Between 1990 and 1998 there was a 33% increase in diabetes prevalence in the United States and, of this increase, 76% occurred in persons between the ages of 30 and 39. Previous studies have failed to provide accurate, yet inexpensive, screening techniques to detect cardiovascular disease in diabetic patients. Our study suggests that ankle brachial indices (ABI) testing may be an effective screening technique for diabetics. Ankles brachial indices (ABI) testing may be an effective screening technique for diabetics. The sole predictive variable reaching significance for the presence of cardiovascular disease was an ABI score <0.90 (p≤0.0001).

**Background** Cardiovascular disease remains the primary cause of diabetes-associated morbidity and mortality. Previous studies have failed to provide accurate, inexpensive, screening techniques to detect cardiovascular disease in diabetics. Ankles brachial indices (ABI) testing may be an effective screening technique for diabetics. Ankles brachial indices (ABI) testing may be an effective screening technique for diabetics.

**Methods and Results** The aim of this 100-subject clinical study was to determine cardiovascular disease prevalence, via perfusion stress testing, in diabetic patients having abnormal ABI (<0.90) and without known heart disease who were referred to the South Carolina Heart Center, Columbia, SC for nuclear perfusion stress testing. Study data were analyzed using frequency and descriptive statistics and 2-sample T-testing. Mean subject age was 62±11 years, ABI 0.76±13, and ejection fraction 60±12%. Perfusion stress testing detected 49 abnormal electrocardiograms, 36 subjects with coronary ischemia, 20 with diminished left ventricular function, and 26 subjects having significant thinning of the myocardium. There were 71 subjects who tested positive for at least one form of cardiovascular disease. The sole predictive variable reaching significance for the presence of cardiovascular disease was an ABI score <0.90 (p≤0.0001).

**Conclusion** Cardiovascular disease may be predicted among diabetic patients via ABI scores and confirmed by nuclear perfusion testing.

**Key Words:** Ankle brachial indices; Cardiovascular disease; Diabetes; Perfusion stress testing
perfusion testing, and underwent a single nuclear perfusion stress test to determine the prevalence of cardiovascular disease.

**ABI**

All study patients had been previously tested to determine their ABI scores, using an 8-mHz Doppler Versa Lab LE (Nicolet Vascular Inc) that has a broad-beam ultrasound probe designed specifically for ABI measurement. Scores were obtained while the subject was supine by recording the systolic blood pressures in the upper extremities (brachial arteries) and in the lower extremities at the dorsalis pedis and posterior tibial arteries. The ABI for each side was calculated by dividing the greater of the 2 ankle systolic readings in the respective leg by the greater brachial pressure. Scores were considered abnormal if the ABI score was 0.90 or less. This stratification has been well established as a valid cut-off point that well correlates with peripheral vascular disease progression although recent research has suggested a diminished pulse wave accuracy below 0.95![12–14] The sensitivity of ABI testing is 90%, and the specificity is 98% for an angiographically defined stenosis of 50% or more in a major artery of the lower extremities.[12–14]

**Perfusion Stress Testing**

All study subjects completed a single nuclear perfusion stress test as a part of the study protocol. A two-detector head, E-Cam (Siemens) was used for each perfusion study. Cardiolite (Bristol-Myers Squibb) was administered as follows in each subject: rest dose: 518 MBq (14 Ci), stress dose: 1,480 MBq (14 Ci). Per protocol, each study subject was injected with the resting dose of Cardiolite after giving informed consent. Subjects then waited 45 min before resting images were acquired, after which they completed a treadmill stress test using a standard Bruce protocol to fatigue or presentation of symptoms. During exercise, the subject was injected with the stress isotope dose upon reaching their target heart rate. Each subject walked a minimum of 60 s post infusion to assure adequate circulation and uptake of the isotope. Study subjects then waited 45 min before stress images were acquired.

**Outcome Measurements**

**Abnormal ECG** Subjects were classified as having an abnormal ECG if they had the presence of any one of, or combination of, the following: ST depression indicative of ischemia (>1 mm), exercise-induced premature ventricular contractions, or exercise-induced atrial fibrillation.

**Ischemic Heart Disease** Coronary ischemia was determined by the interpreting physician and was confined to reversible scan perfusion defects. Ischemic severity ranged from mild to severe; however all cases of evident ischemia were classified as positive.

**Diminished Left Ventricular (LV) Function** Diminished LV function was determined by the interpreting physician who estimated the LV ejection fraction (LVEF) as well as observing for myocardial wall motion abnormalities. LVEF was calculated using the Mandrake computer processing system, based on the time and energy level of the isotope within the ventricle. Diminished LV function is defined as LVEF ≤45% as determined by single photon emission computed tomography.

**Myocardial Wall Thinning** Myocardial wall thinning was determined by the absence of isolate uptake within a specific wall region of the myocardium. Significant thinning of the myocardial wall, as observed during perfusion imaging, is generally a result of a former MI if the reduction in uptake remains fixed. Conversely, if the uptake reduction fluctuates, ischemia is likely present. A significant thinning of the myocardium was determined by the interpreting physician while analyzing scan results.

**Statistical Analysis**

Study population data were examined using descriptive statistics allowing for a comprehensive, detailed analysis of the variables among study patients. Statistical significance (≥0.05) among measured variables was assessed to determine if a significant variance was observed between subjects having any form of cardiovascular disease and those without disease, and within specific stratified cardiovascular disease characteristics (ischemia, abnormal ECG, myocardial wall thinning, diminished LV function). Descriptive statistics and 2-sample T-testing procedures were conducted on stratified data. Statistical analyses were performed using the Statistix 7 computer statistical application within the South Carolina Heart Center, Department of Investigator Initiated Research.

**Results**

Of the 100 patients having a diagnosis of both type 2 diabetes and an abnormal ABI test who were referred to our practice by their primary care physician for participation in this study, 56 were male and 78 were Caucasian (22 were African American). All study subjects were free of known cardiovascular disease at the time of enrollment. Population mean data were age 62±11 years (range 33–88), ABI 0.76±0.13 (range 0.36–0.89), and LVEF 60±13% (range 32–90) (Table 1). Diagnostic results of perfusion stress testing for the population whole are as follows: 49 subjects had an abnormal ECG, 36 subjects had coronary ischemia, 20 subjects had diminished LV function, and 26 subjects had observable thinning of the myocardial wall. In total, 71 of the 100 subjects tested positive for at least 1 form of cardiovascular disease.

When analyzing the measured variables by disease vs non-disease classification (Table 2), only an abnormal ABI score reached a significant association with the presence of cardiovascular disease (p≤0.0001).

Male subjects (Table 3) had ischemic heart disease detected at a 2:1 ratio and were statistically more likely to show ischemia than females (p=0.01). Males were also found to have diminished LV function at a 3:1 ratio compared with females (p=0.04), and myocardial wall thinning at a 2:1 ratio (p=0.02).
Table 2 Diabetic Patients With Abnormal Ankle Brachial Indices by Cardiovascular Disease Diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>No disease</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>43/28</td>
<td>13/16</td>
</tr>
<tr>
<td>Race (Caucasian/Afr. American)</td>
<td>55/16</td>
<td>23/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±10</td>
<td>59±13</td>
</tr>
<tr>
<td>Ankle brachial indices</td>
<td>0.74±0.14</td>
<td>0.82±0.07</td>
</tr>
<tr>
<td>Exercise time (s)</td>
<td>40±135</td>
<td>48±160</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>122±31</td>
<td>122±31</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mmHg)</td>
<td>165±30</td>
<td>161±22</td>
</tr>
<tr>
<td>Peak diastolic blood pressure (mmHg)</td>
<td>81±13</td>
<td>82±10</td>
</tr>
<tr>
<td>METS</td>
<td>7.7±2</td>
<td>8.2±3</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59±13</td>
<td>6±11</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.

Table 3 Disease Characteristics by Gender

<table>
<thead>
<tr>
<th>Disease</th>
<th>Male</th>
<th>Female</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary ischemia</td>
<td>24</td>
<td>12</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>32</td>
<td>32</td>
<td>0.73</td>
</tr>
<tr>
<td>Diminished LV function</td>
<td>15</td>
<td>5</td>
<td>0.04</td>
</tr>
<tr>
<td>Normal LV function</td>
<td>41</td>
<td>39</td>
<td>0.89</td>
</tr>
<tr>
<td>Myocardial wall thinning</td>
<td>38</td>
<td>36</td>
<td>0.13</td>
</tr>
<tr>
<td>Normal myocardial wall</td>
<td>38</td>
<td>36</td>
<td>0.13</td>
</tr>
</tbody>
</table>

All values are expressed as number (%). LV, left ventricular.

Discussion

Clinical Implications

Our study results suggest that an abnormal ABI score (<0.90) may hold predictive value in assessing the diabetic patient for the presence of cardiovascular disease. This non-invasive and inexpensive screening procedure may be capable of predicting cardiovascular disease before the presentation of symptoms or an acute event in this vulnerable patient population. ABI screening, when combined with perfusion stress testing, becomes highly effective in detecting cardiovascular disease among diabetics who are recognized to have an inherently elevated risk for cardiovascular disease. Igarashi et al, in a similar study of non-diabetic subjects, found that the addition of ABI testing helped to stratify patients with multiple risk factors. It is hypothesized that the stratification of diabetic subjects using ABI, in conjunction with additional risk factors, would also be useful and should be the focus of future research.

The PARTNERS trial revealed that 56% of non-diabetic subjects with abnormal ABI have evidence of cardiovascular disease, and also found diabetes prevalence documented in more patients with peripheral vascular disease alone compared with cardiovascular disease alone. It was our hypothesis, and the goal of this study, to determine if the prevalence of cardiovascular disease would increase within a diabetic population. We detected cardiovascular disease in 71% of our study subjects, although the PARTNERS study used different parameters to confirm cardiovascular disease.

With the number of diabetic patients increasing rapidly it becomes imperative that we implement standardized screening for early stage cardiovascular disease detection. ABI screening, in combination with perfusion stress testing, appears a viable method of safely and cost-effectively screening this vulnerable cohort of patients.

Our study provides new information about the diabetic patient without known cardiovascular disease. Diabetic patients, with or without cardiovascular disease symptoms, should undergo an ABI test because an abnormal result is highly predictive of the presence of one or more forms of cardiovascular disease.

Our study also shows that males in this cohort of patients tend to be more ischemic, have diminished LV function, and have more instances of myocardial wall thinning than do females. These findings add justification for earlier screening, potentially facilitating detection of cardiovascular disease at a subclinical level thereby improving prognosis and treatment outcomes.

Study Limitations

The principal goal of this study was to determine the prevalence of cardiovascular disease in a specific cohort of patients via ABI screening and perfusion stress testing. Data from diabetic subjects who have had a nuclear perfusion study and have normal ABI values would have provided a more robust picture by acting as a control group. Future research should focus on the prevalence rates of cardiovascular disease among diabetic subjects without an abnormal ABI result for comparative value.

Conclusion

Our clinical study supports that ABI screening, in conjunction with nuclear perfusion stress testing, is an efficacious modality for detecting cardiovascular disease among a diabetic patient cohort. Additionally, the results of this study indicate that traditional risk indicators such as age, blood pressure, LVEF, and exercise capacity may not hold significant predictive value within this patient subgroup. With a 71% cardiovascular disease prevalence rate among our diabetic population we would encourage ABI screening and, if warranted, perfusion stress testing of all diabetic patients in an effort to detect cardiovascular disease before the onset of symptoms, acute events, or sudden cardiac death.

Acknowledgment

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References


