Reliability of Two Ankle-Brachial Index Methods to Predict Silent Lacunar Infarcts: A Population-Based Study in Stroke-Free Older Adults (the Atahualpa Project)

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Abstract

Individuals with an abnormal ankle-brachial index (ABI) are four times more likely to have a silent lacunar infarct (SLI), but reliability of ABI in predicting the presence of these lesions has not been estimated yet.

We compared two methods of calculating ABI to assess their reliability in predicting SLIs. Stroke-free Atahualpa residents aged ≥ 60 years underwent MRI of the brain and ABI determinations. Persons with ABI ≥ 1.4 were excluded. Using receiver operator characteristic curve analysis, we calculated the reliability of the traditional as well as an alternative ABI method to identify individuals with SLI. The traditional ABI uses the higher systolic pressure of either the dorsalis pedis or the posterior tibial arteries as the numerator, whereas the alternative ABI uses the lower pressure.

Of the 247 participants, 38 (15%) had traditional and 95 (38%) had alternative ABIs ≤ 0.9 . Twenty-one individuals had SLI. Traditional and alternative ABIs ≤ 0.9 identified 9 and 13 individuals with SLI, respectively. The traditional ABI had sensitivity of 42.9% (22.6–65.6%) and specificity of 87.2% (81.9–91.1%). The alternative ABI had sensitivity of 61.9% (38.6–81%) and specificity of 63.7% (57–69.9%). The area under the curve for the predictive value of SLI was 0.65 (0.54–0.76) for the traditional and 0.63 (0.52–0.74) for the alternative ABI ≤ 0.9 .

The ABI is moderately reliable for identifying candidates for MRI screening in studies assessing the burden of SLI in older adults. The traditional ABI seems to be more suitable for this purpose.

Keywords

- ▶ ankle-brachial index
- ▶ alternative ankle-brachial index
- ▶ peripheral artery disease
- ▶ silent lacunar infarcts
- ▶ magnetic resonance imaging
- ▶ population-based studies
- ▶ developing countries

The burden of stroke is gradually increasing in many low- and middle-income countries.¹ Epidemiologic data suggest that lacunar infarcts are one of the most frequent stroke subtypes in these regions.^{2,3} However, many patients with lacunar infarcts do not present with an overt stroke syndrome, but rather have a subclinical, silent lesion that

is only identifiable on magnetic resonance imaging (MRI) of the brain.⁴ Despite being silent, these infarcts increase the risk of overt stroke and vascular dementia.⁵ Therefore, prompt detection of individuals with silent lacunar infarcts (SLIs) is important to initiating interventions aimed at reducing the risk of future events.

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Diagnosis of SLI requires the use of MRI of the brain, which is frequently not available in rural communities of developing countries. Therefore, identification of reliable screening diagnostic tools that may help identify candidates for MRI screening would be useful. Preliminary findings from our group showed that older adults with an abnormal ankle-brachial index (ABI) are almost four times more likely to have an SLI.⁶ Though the ABI is primarily used to detect persons with suspected peripheral artery disease, there is increasing evidence that abnormal ABI determinations also correlate with coronary artery disease and stroke.^{7,8} However, more information on the reliability of the ABI as a predictor of SLI is needed.

In this study, we used both the traditional and the alternative ABIs for this purpose. The traditional ABI uses the higher systolic pressure of either the dorsalis pedis or the posterior tibial arteries as the numerator, whereas the alternative ABI uses the lower; in both methods, the higher of the systolic pressure in both the arms is used as the denominator.⁹ The alternative ABI has been shown to increase the sensitivity of the test to detect outcomes at the expense of a reduced specificity.^{10,11}

Methods

The study was conducted in Atahualpa, a coastal rural community in Ecuador, where previous epidemiologic studies on cardiovascular diseases have been performed.^{12,13} All Atahualpa residents aged ≥ 60 years identified during yearly door-to-door surveys from 2012 to 2015 were invited to the community center of the Atahualpa Project for cardiovascular risk assessment and ABI determination, and were offered an MRI of the brain that was performed at Hospital-Clínica Kennedy, Guayaquil. Reasons for not participating included refusal to sign the informed consent, severe disability, claustrophobia, and contraindications for MRI or ABI determinations. The Institutional Review Board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the protocol and the written informed consent.

Demographics and cardiovascular risk factors were assessed through interviews and procedures previously described in the Atahualpa Project. The cardiovascular health (CVH) status was evaluated by the use of the seven metrics proposed by the American Heart Association, including smoking status, body mass index, physical activity, diet, blood pressure (BP), fasting glucose, and total cholesterol blood levels. Each metric was categorized as ideal, intermediate, or poor, and the CVH status was classified as poor if at least one metric was in the poor range.¹⁴ To recognize, and further exclude, patients with overt strokes, rural physicians screened all persons with the use of a validated field questionnaire, and then certified neurologists confirmed the diagnosis.

MRIs were performed with a Philips Intera 1.5T machine (Philips Medical Systems, Eindhoven, the Netherlands) at Hospital-Clínica Kennedy, Guayaquil, following a well-defined protocol described elsewhere.¹⁵ In brief, MRI included two-dimensional multislice turbo spin echo T1-weighted, fluid-

attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a T1-weighted sequence oriented in the sagittal plane. We used the preestablished brain imaging package delivered by the manufacturer to homogenize applicability by technicians; slice thickness was 5 mm with 1-mm gap between slices. Two readers, blinded to clinical data, independently reviewed all MRIs and discrepancies were resolved by consensus. Interest focused on the presence of SLI, defined as fluid-filled cavities measuring 3 to 15 mm located in the territory of a perforating arteriole.⁴

The protocol used for ABI determinations in Atahualpa residents followed the recommendations of the American Heart Association and has been detailed elsewhere.⁶ In brief, with persons resting in the supine position under comfortable room temperature levels, BPs were measured in both the arms and legs following a counterclockwise sequence: right arm, right posterior tibial, right dorsalis pedis, left posterior tibial, left dorsalis pedis, and left arm. The traditional ABI uses the highest systolic pressure of either the dorsalis pedis or the posterior tibial arteries as the numerator, whereas the alternative ABI uses the lowest; in both methods, the highest of the systolic pressure in the both arms is used as the denominator, and the lowest ABI between the two ankles was used for classifying purposes.¹⁰

Statistical analyses were performed by using STATA version 14 (College Station, TX). Reliability of the traditional as well as the alternative ABI to predict the presence of SLI was assessed by calculating its sensitivity and specificity, as well as its positive (PPV) and negative predictive values (NPV) (with their corresponding 95% confidence intervals [CI]). For this, we used the preestablished cutoff for ABI (≤ 0.9). Using receiver operator characteristics curve analysis, we calculated the area under the curve (AUC) for the predictive value of SLI of traditional and alternative ABI determinations.

Results

Of 385 eligible candidates, 293 (76%) underwent both MRI of the brain and ABI determinations. Of these, 26 were excluded for a diagnosis of overt stroke, and 20 because they had an ABI ≥ 1.4 (suggestive of noncompressible arteries).

Mean age of the 247 participants was 69 ± 8 years, 154 (62%) were women, 198 (80%) had primary school education only, and 174 (70%) had a poor CVH status, with a mean of 1.2 ± 1 poor metrics per person. Individual health metrics more often in the poor range were BP in 110 (44%) cases, fasting glucose in 75 (30%), and the body mass index in 46 (19%). SLIs were noticed in 21 individuals (9%), with a Kappa coefficient for inter-rater agreements of 0.90.

Using the traditional ABI method, mean ABI values were 1.04 ± 0.13 for right (range 0.60–1.37) and 1.05 ± 0.12 for left (range 0.59–1.39) legs. Thirty-eight (15%) persons had an ABI ≤ 0.90 (bilateral in 11); the remaining 209 (85%) persons had ABIs between 0.91 and 1.39. Intraobserver reliability for the above categories of ABI in 125 (50%) randomly selected persons was good ($k = 0.71$, 95% CI: 0.55–0.86, 90% agreement). Nine (24%) out of the 38 individuals with a traditional

ABI ≤ 0.9 and 12 (6%) out of the 209 with a normal traditional ABI had an SLI. These numbers indicated for the traditional ABI a sensitivity of 42.9% (95% CI: 22.6–65.6%), a specificity of 87.2% (95% CI: 81.9–91.1%), a PPV of 0.24 (95% CI: 0.12–0.41), and an NPV of 0.94 (95% CI: 0.90–0.97). The AUC for the predictive value of SLI using the traditional ABI ≤ 0.9 was 0.65 (95% CI: 0.54–0.76).

Using the alternative ABI method, mean ABI values were 0.99 ± 0.10 for right (range 0.36–1.33) and 0.97 ± 0.13 for left (range 0.46–1.29) legs. Ninety-five (39%) persons had an ABI ≤ 0.90 (bilateral in 36); the remaining 152 (61%) persons had ABIs between 0.91 and 1.39. Intraobserver reliability for the above categories of ABI in the same 125 (50%) randomly selected persons was good ($k = 0.68$, 95% CI: 0.59–0.78, 85% agreement). Thirteen (14%) out of the 95 individuals with an alternative ABI ≤ 0.9 and 8 (5%) out of the 152 with a normal alternative ABI had an SLI. These numbers indicated for the alternative ABI a sensitivity of 61.9% (95% CI: 38.6–81%), a specificity of 63.7% (95% CI: 57–69.9%), a PPV of 0.14 (95% CI: 0.08–0.23), and an NPV of 0.95 (95% CI: 0.90–0.98). The AUC for the predictive value of SLI using the alternative ABI ≤ 0.9 was 0.63 (95% CI: 0.52–0.74).

Discussion

In this population-based study of community-dwelling older adults living in a rural Latin American population, a traditional ABI determination below the established cutoff value of ≤ 0.9 is moderately reliable for identifying candidates for MRI screening by detecting 43% of cases of SLI, with a specificity of approximately 87%. Using the alternative ABI method, the sensitivity increases to 62% at the expense of lowering the specificity to approximately 64%. Comparison of the reliability of the traditional versus the alternative ABI for predicting the presence of SLI showed overlap in the confidence intervals of most of the measures of performance of these tests with the exception of the specificity, which was better for the traditional ABI (► **Table 1**). In other words, the alternative ABI detected one more case of SLI than the traditional ABI per every 15 additional MRIs performed. Given the cost of MRI examinations and the problems inherent to transporting older adults from remote villages to urban centers, the advantage

in the sensitivity of the alternative ABI determinations is not likely to be cost-effective.

As noted, some studies have found a higher prevalence of SLI among individuals with abnormal ABI determinations, even after adjusting for relevant confounders; in such studies, traditional ABI determinations were used.^{6,16} The alternative ABI has long been used to improve the noninvasive recognition of patients with peripheral arterial disease.^{10,17,18} More recently, the alternative ABI has been shown to be more sensitive than the traditional ABI for the detection of persons at risk for developing cardiovascular event that would have been missed with the use of the traditional ABI.¹¹ However, comparison of the reliability of the traditional as well as that of the alternative ABI to predict the occurrence of SLI has not yet been investigated so far.

The relationship between abnormal ABI determinations and SLI is not completely understood, because peripheral artery disease is related to damage to the medium-to-large vessels and SLIs are associated with cerebral small vessel disease. However, some cardiovascular risk factors such as arterial hypertension may simultaneously affect different arterial beds and might be responsible for both conditions.¹⁹ In addition, a sizable proportion of cerebral infarcts fulfilling the operational definition of “lacunar” are not related to small vessel disease but to artery-to-artery emboli originating in plaques located in the carotid arteries or to intracranial artery stenosis.^{20,21}

We did not perform angiography to confirm the diagnosis of peripheral artery disease in individuals with a low ABI and did not evaluate the carotid arteries to look for stenosis or plaques in patients with SLI. These, together with the relatively small sample size, are limitations of this study. However, the population-based design with unbiased enrollment of participants and the adequate levels of inter- and intrareader agreements for MRI findings of interest and ABI determinations argue for the strength of our results. Further longitudinal studies are needed to confirm the role of traditional or alternative ABI determinations in mass screening of MRI candidates for detection of individuals with SLI at risk for overt strokes and vascular cognitive impairment.

Table 1 Estimates of sensitivity, specificity, PPV and NPV, and ROC curve analyses showing reliability of the traditional versus the alternative ABI determination to predict the presence of SLIs

	Sensitivity	Specificity	PPV	NPV	AUC
Traditional ABI	42.9 (22.6–65.6)	87.2 (81.9–91.1)	0.24 (0.12–0.41)	0.94 (0.90–0.97)	0.65 (0.54–0.76)
Alternative ABI	61.9 (38.6–81)	63.7 (57–69.9)	0.14 (0.08–0.23)	0.95 (0.90–0.98)	0.63 (0.52–0.74)

Abbreviations: ABI, ankle-brachial index; AUC, area under the curve; NPV, negative predictive values; PPV, positive predictive values; ROC, receiver operator characteristics; SLI, silent lacunar infarct.

Note: Numbers in parenthesis correspond to 95% confidence intervals.

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