Research Article

Insights of Cardiovascular Pharmacology Research

Ankle-Brachial Index: A Simple and Inexpensive Screening Test for Coronary Artery Disease (ABI goes beyond the foot)

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Submitted: 04 Mar 2022; **Accepted:** 15 Mar 2022; **Published:** 28 Mar 2022

Citation: *Reza Golchin Vafa, Bardia Zamiri, Mohammadhossein Rahmani , Mohammadjavad Mehdizadeh Parizi , Reza Heydarzadeh, Amin Ahmadi, Mohammad Montaseri, Javad Kojur, (2022). Ankle-Brachial Index: A Simple and Inexpensive Screening Test for Coronary Artery Disease (ABI goes beyond the foot) Running title: ABI for Coronary Artery Disease Screening. Insig Cardio Vasc Phar Res, 2(1), 17-22.*

Abstract

Background: *Coronary artery disease (CAD) is the leading cause of death in the world. In this study we assessed ankle-brachial index (ABI) as a screening tool for CAD.*

Method: *Between 2019 and 2020, large cross-sectional population-based study of 4207 new patients referred to cardiovascular Clinic was enrolled. The patients underwent selective coronary angiography via radial artery approach. ABI was calculated for all patients. We compared ABI with the results of coronary angiography to determine the specificity and sensitivity of ABI as a screening tool for CAD.*

Results: *Abnormal ABI was significantly more frequent in patients with proven severe CAD (893, 54.8%) than in patients with proven mild CAD (33, 4.7%) or no CAD (94, 5.3%). The specificity of ABI was 95.3%, and its sensitivity was 54.8%. ABI was associated with risk factors such as smoking, male gender, hypertension, diabetes mellitus and dyslipidemia.*

Conclusion: *ABI can be used as a screening test to rule out CAD with 95.3% specificity. We need to consider risk factors other than ABI to increase screening sensitivity. A multidimensional scoring system should consider risk factors and other noninvasive tests in addition to ABI to develop and ideal screening system for CA. (Clinical trial registration number NCT04667832)*

Keywords: Ankle brachial index, Coronary artery disease, Sensitivity, Specificity.

Introduction

Atherosclerosis, a chronic disease that leads to the deposition of plaques within the arterial system, is the most common cause of coronary artery disease (CAD) and peripheral artery disease (PAD). Atherosclerosis begins in fetal life, and early detection is crucial for the prevention of drastic events [1-3]. Coronary artery disease is the leading cause of death worldwide, and knows no borders. As the risk factors for CAD increase worldwide, the prevalence of CAD will also rise [4, 5]. Male sex, family history of CAD, aging, sedentary lifestyle, smoking, unhealthy diet, hypertension, obesity, dyslipidemia and diabetes mellitus are risk factors that are strongly related with CAD [6, 7].

Studies have shown that reducing risk factors plays an important role in decreasing CAD [8]. To prevent this disease we need to assess the risk of future CAD in every patient referred for cardiovascular care. As the risk increases, more intense efforts will be needed to prevent CAD [9]. However, risk estimation for patients is not simple, and each of the several systems for risk estimation has its own limitations. For example, the Framingham risk score has limitations for age. Although many of these systems have been modified to consider new risk factors, they do not meet current needs. A new multidimensional risk estimation system is needed to improve the prevention of CAD [10-12].

Ankle-brachial index (ABI) can be used to screen for PAD, with over 90% sensitivity compared to angiography [13]. It has been demonstrated that ABI correlates with the extent of CAD. Pa-

tients with lower ABI were found to have more diseased coronary arteries [14]. In addition, the prevalence of CAD was twice as high in individuals with abnormal ABI (<0.9) compared to people with normal ABI (>0.9) [15]. Abnormal ABI was related with more cardiovascular outcomes in patients hospitalized for acute coronary syndrome after 1 year of follow-up. The frequency of vascular death was also higher in individuals with abnormal ABI [16]. Moreover, ABI is believed to be associated with risk factors for atherosclerosis [17].

Nevertheless, some studies found no significant correlation between ABI and CAD [19-21]. No studies to date have investigated the relationship between CAD and ABI considering novel risk factors such as high-sensitivity CRP (hs-CRP). Among earlier studies, there appears to be no consensus regarding whether inter-arm systolic blood pressure difference is associated with CAD. In this study we assessed ABI as a screening tool for both PAD and CAD. We hypothesized that ABI provides information that goes beyond the foot and can be used as an indicator of systemic atherosclerosis, e.g. CAD. We also used hs-CRP to screen for CAD. In addition, this study examined the association between CAD and inter-arm systolic pressure difference.

Methods

This cross-sectional study was conducted between 2019 and 2020. The inclusion criterion was new patient referred to Professor Kojuri Cardiovascular Clinic in Shiraz, Iran (email: kojurij@yahoo.com, webpage: http://kojuriclinic.com). The exclusion criteria were deep vein thrombosis, lower extremity injury that caused severe pain, and inability to remain supine. Patients with ABI more than 1.4 were also excluded. Complete history was noted and physical examination findings were recorded for all patients. Risk factors such as smoking, hypertension, dyslipidemia, diabetes mellitus, age and gender were considered. We also recorded triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, HbA1c and hs-CRP for all patients, and documented blood pressure and electrocardiographic findings for all patients.

cholesterol. Diabetes mellitus was diagnosed according to the 2019 ADA guidelines [22]. Hypertension were defined according to the ACC/AHA 2017 guidelines [23]. Triglyceride levels higher than 200 mg/dL, total cholesterol more than 200 mg/dL, LDL cholesterol more than 100 mg/dL, HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women, HbA1c more than 6.5% and hs-CRP more than 2 mg/L were considered abnormal. Patients with hs-CRP more than 10 mg/L were excluded due to the possibility of acute inflammation. Smoking was defined as regular tobacco smoking or past history of smoking within 3 months before the study [24-29]. If noninvasive studies yielded no evidence of abnormal findings, this was considered absence of CAD. Patients with strongly positive results in noninvasive studies underwent selective coronary angiography via radial artery approach by an expert interventional cardiologist. Angiography videos were reviewed by a team of expert cardiologists. Based on the results, patients were classified as having proven mild CAD if stenosis was less than 50%, or proven severe CAD if stenosis was more than 50%.

ABI was determined in all patients with the Huntleigh Dopplex Ability Automatic Ankle Brachial Index System (Cardiff, UK), which uses Doppler ultrasound to measure blood pressure. The appropriate cuffs were selected for each patient, and the patient lay supine for 30 min before starting the test. The ankle and arm cuffs were attached directly to the patient's skin. Blood pressure was recorded in both the left and right limbs. An ABI less than 0.9 was considered abnormal, and values between 0.9 and 1.4 were considered normal. Patients with both right and left ABI between 0.9 and 1.4 were classified as having normal ABI. Patients with a right and/or left ABI less than 0.9 were considered to have abnormal ABI. We also calculated inter-arm systolic pressure difference for each patient; a difference greater than 10 mmHg was considered abnormal.

The study was double-blinded. The team of cardiologists who recorded the results of coronary angiography were blinded to the patients' ABI. The statisticians did not receive information about the ABI values or coronary angiography findings. For blinding, we used alphabetical order for each group of patients with or without coronary artery disease. Patients with proven mild CAD were designated with the letter A, and patients with proven severe CAD were designated with the letter B. We also used alphabetical order for normal or abnormal ABI. Patients with abnormal ABI were designated with the letter C, and patients with normal ABI were designated with the letter D.

For statistical analyses we used IBM SPSS software version 25. Independent-sample t tests and one-way ANOVA were used for parametric variables. The Mann-Whitney U test and Kruskal-Wallis test were used for nonparametric data. Values of $p<0.05$ were considered significant. All patients were informed about the details of this research, and provided their written informed consent. Patients who declined to participate in the study were excluded. The protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences under code number: IR.SUMS.MED.REC.1398.437. All methods were performed in accordance with the Helsinki ethics guidelines and regulations.

Results

During the study period, 4207 new patients were referred to the cardiovascular clinic. 91 patients were excluded based on the exclusion criteria, and we calculated ABI for the remaining 4116 patients (2179 women [52.9%] and 1937 men [47%]). Mean age of the patients in this study was 63±12.8 years. The prevalence of other risk factors were hypertension in 2706 (65.7%), diabetes mellitus in 1152 (27.9%), dyslipidemia in 813 (19.7%), and smoking in 585 (14.2%).

There were 1787 patients (43.4%) with no CAD based on noninvasive tests. Of the 2329 patients (56.5%) who underwent coronary angiography, 699 (16.9%) were considered to have proven mild CAD, and 1630 (39.6%) were considered to have proven severe CAD.

ABI was calculated for all patients before angiography. There were 1020 patients (24.7%) with abnormal ABI and 3096 patients (75.2%) with normal ABI.

Abnormal ABI in patients with proven severe CAD (893, 54.8%) was significantly more frequent than in patients with proven mild CAD (33, 4.7%) or no CAD (94, 5.3%) (p<0.001). There was no significant difference in ABI between patients with proven mild CAD (33, 4.7%) and no CAD (94, 5.3%) (p=0.583). There was no relationship between abnormal inter-arm systolic pressure difference and the severity of CAD. In patients who underwent coronary angiography there was no significant difference in the frequency of abnormal inter-arm systolic pressure difference between those with proven mild CAD (97, 13.8%) and proven severe CAD (242, 14.7%) (p=0.55) (Table 1, Figure 1).

Table 1: Comparison of Normal ABI, Abnormal ABI and Inter-Arm Pressure Differences Among Patients with No Cad, Mild or Severe Cad

	No CAD	Proven mild CAD	Proven severe CAD
Abnormal ABI, n (%)	94 (5.3%)	33 (4.7%)	893 (54.8%)
Normal ABI, n (%)	1693(94.7%)	666 (95.3%)	737 (45.2%)
Inter-arm systolic pressure difference > 10 mmHg (n, %)	282 (15.7%)	97 (13.8%)	242 (14.7%)

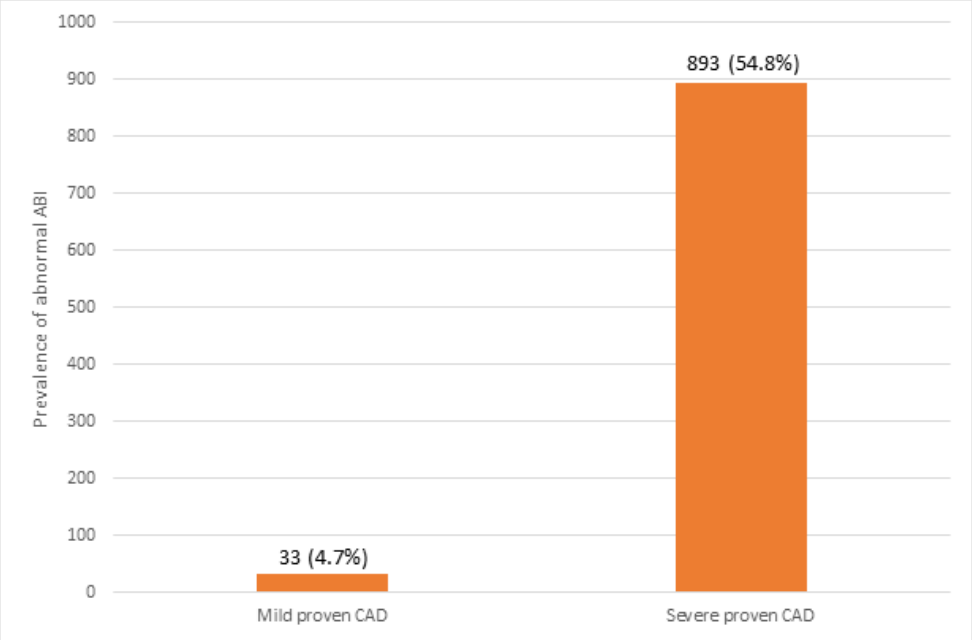

Figure 1: Prevalence of abnormal ABI in patients with proven mild or severe CAD

We compared the results of ABI with the results of angiography in patients who underwent this procedure. The sensitivity of ABI was 54.7% and its specificity was 95.2%. Positive predictive value was 96.4%, and negative predictive value was 47.7%. Positive likelihood ratio was 11.39, and negative likelihood ratio was 0.47 (Table 2).

Table 2: Comparison of ABI and Coronary Angiography Results in Patients Who Underwent Coronary Angiography

	Abnormal ABI	Normal ABI
Mild proven CAD	33	666
Severe proven CAD	893	737

Abnormal ABI was more frequent in older than in younger patients (p<0.001, rho=−0.227). Among patients with abnormal ABI, smoking was more frequent (225, 22.1%) than in patients with normal ABI (360, 11.6%) (p<0.001). More patients with abnormal ABI had diabetes mellitus (441, 43.2) than patients with normal ABI (711, 23%) (p<0.001). Hypertension was more frequent in patients with abnormal ABI (717, 70.3%) than in patients with abnormal ABI (1989, 64.2%) (p<0.001). Dyslipidemia was significantly more frequent in patients with abnormal ABI (230, 22.5%) than in patients with normal ABI (583, 18.8%) (p=0.011). Abnormal ABI was more frequent in men (507, 26.2%) than women (513, 23.5%), with a borderline significant p value (p=0.051) (Table 3).

Table 3: Comparison Risk Factors Between Patients with Abnormal and Normal ABI

	Abnormal ABI	Normal ABI	p value
Mean age ± SD	69 ± 12	63 ± 13	<0.001
Male, n (%)	507 (49.7%)	1430 (46.2%)	0.051
HTN, n (%)	717 (70.3%)	1989 (64.2%)	<0.001
DM, n (%)	441 (43.2%)	711 (23%)	<0.001
Smoker, n (%)	225 (22.1%)	360 (11.6%)	<0.001
Dyslipidemia, n (%)	230 (22.5%)	583 (18.8%)	0.01

Abnormal hs-CRP values were more frequent in patients with abnormal ABI than in patients with normal ABI, but the p value was not statistically significant (p=0.611).

We found that high inter-arm systolic pressure difference had a significant association with abnormal ABI. The prevalence of inter-arm systolic pressure difference >10 mmHg was 222 (21.8%) in patients with abnormal ABI, and 394 (12.7%) in patients with normal ABI (p<0.001).

Discussion

Although previous studies have investigated the association between ABI and CAD in patients for whom this disease was suspected, the present study focused on testing ABI as a screening tool in the general population. Our study population included not only patients at high risk for CAD but also those with a low probability of having this disease. In their metaanalysis, Fowkes et al. concluded that ABI was associated with future CAD independently of the Framigham risk score [30]. Papa et al. found that abnormal ABI was associated not only with the severity of CAD but also with the extent of the disease: abnormal ABI was more frequent in patients with multi-artery disease than in those with single-arterial disease [31].

Lee et al. found that myocardial infarction, stroke and death were more frequent in patients with abnormal ABI than those with normal ABI during a 3-year follow-up period [32]. Liu et al. suggested that ABI can predict major adverse cardiac events and all-cause mortality in patients with CAD, given that the rates of major adverse cardiovascular events and all-cause mortality were higher in patients with abnormal ABI [33]. In the present study, although abnormal ABI did not differ significantly between patients with no CAD and those with proven mild CAD, abnormal ABI was significantly more prevalent in our patients with proven severe CAD than in those with proven mild or no CAD. This finding suggests that ABI is potentially useful as a screening test for severe CAD. Our calculations yielded a high specificity (95.3%) but low sensitivity (54.7%) for ABI. The high specificity means that ABI can potentially be used as a reliable screening test to rule out CAD.

However, the low sensitivity indicates that diagnostic tests for CAD should consider other risk factors in addition to ABI. For example, adding diabetes mellitus increased sensitivity to 96.0%. Hatmi et al. showed that ABI had 99.7% specificity and 64% sensitivity for diagnosing CAD [34]. The difference in sensitivity between studies may be due to differences in the populations. Hatmi et al. selected populations in which there was a high suspicion of CAD, whereas our sample was drawn from a more general population.

In the present study, abnormal ABI showed a significant association with most of the traditional CAD risk factors. We found that abnormal ABI was significantly associated with male gender, age, smoking, hypertension, diabetes mellitus, and dyslipidemia. Sadeghi et al. also found that cardiovascular risk factors were significantly more prevalent in patients with abnormal ABI than in those with normal ABI: they reported abnormal ABI to be significantly associated with diabetes mellitus, hypertension, hyperlipidemia and smoking [17]. Wild et al. found that low ABI was associated with increasing risk of cardiovascular disease independently of traditional risk factors and metabolic syndrome. These results, together with the present findings, also suggest that ABI can be used for risk assessment in patients independently of their cardiovascular risk factors [35].

In the present study we calculated inter-arm systolic pressure difference and analyzed its possible association with ABI. Kim et al. found that 10-year cardiovascular risk as estimated by the Framingham risk score correlated significantly with inter-arm systolic pressure difference [36]. Tokitsu et al. reported that inter-arm systolic pressure difference was associated with the severity of CAD, i.e. high inter-arm systolic pressure difference correlated with Gensini score [37]. A cohort study of 3350 patients showed that inter-arm systolic pressure difference was associated with higher cardiovascular mortality (hazard ratio 1.91, 95% confidence interval 1.19–3.07) [38]. Despite these earlier reports, we found no association between inter-arm systolic pressure difference and CAD, although we did find that abnormal ABI was associated with abnormal inter-arm systolic pressure difference. It thus appears likely that PAD can be detected by the inter-arm systolic pressure difference as well as by ABI.

Aso et al. found no association between hs-CRP and ABI in about 100 patients with type 2 diabetes [39]. A study of about 2000 participants showed that hs-CRP had a weak but statistically significant negative correlation with ABI (p=0.014, rho=−0.077) [40]. Thejaswini et al. found that ABI had a significant correlation with hs-CRP in patients with type 2 diabetes mellitus (p<0.001, r=−0.560) [41]. We found no correlation between hs-CRP and ABI. When we assessed the difference in ABI between patients with hs-CRP >2.0 mg/L and <2.0 mg/L, we found that abnormal ABI was more prevalent in the former, although the difference between groups was not statistically significant. This may be due to the number of participants in the present study; additional studies are needed to provide more data.

Conclusions

In this large population-based study we hypothesized that ABI would show a significant association with CAD in patients referred to a cardiovascular clinic. ABI had high specificity for detecting CAD, and can be used to rule out CAD. Abnormal ABI was associated with male gender, aging, hypertension, smoking, diabetes mellitus, and hyperlipidemia. Future studies should focus on testing ABI along with other risk estimation systems to design a multidimensional system for CAD screening.

Study limitations

Our study design was cross-sectional, so we were not able to assess the causal relationship between CAD and abnormal ABI. We also note that use of a more accurate method to determine the extent and severity of CAD is advisable. Further prospective cohort studies are needed to evaluate the exact role of ABI in detecting CAD.

Conflict of interest :

Authors declared that none of them have conflict of interest

Author contribution:

RG: Study conduction, gathering data, randomization, statistical analysis, writing article
BZ: Gathering data, randomization
MR: Study conduction, gathering data, randomization
MMP: Gathering data, randomization
RH: Study conduction, randomization, statistical analysis, writing article
AA: Gathering data, randomization
MM: Gathering data, randomization
JK: Main researcher, study idea and protocol, study conduction, gathering data, randomization, statistical analysis, writing article

Protocol approval:

The protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences under code number: IR.SUMS.MED.REC.1398.437. All methods were performed in accordance with the Helsinki ethics guidelines and regulations.

Acknowledgments

We thank Shiraz University of Medical Sciences for providing ethical review and approval of our protocol, and K. Shashok (AuthorAID in the Eastern Mediterranean) for improving the use of English in the manuscript. This manuscript was submitted as a pre-print in the link "https://www.researchsquare.com/article/rs-871459/v1. [42]

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