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ABSTRACT

Background: Diagnosing peripheral arterial disease (PAD) can be challenging owing to medial arterial calcification (MAC) in patients with diabetes mellitus (DM) and chronic kidney disease (CKD). Current bedside tests, such as the ankle-brachial index and toe-brachial index, are often insufficient. The maximal systolic acceleration (ACC_{max}) is a velocimetric Doppler-derived parameter and could be a new promising test in the diagnostic workup of these patients. The primary aim of this study was to evaluate the diagnostic performance of the ACC_{max} to detect PAD.

Methods: A retrospective cohort study was performed in a tertiary referral hospital. Patients ≥18 years old with suspected PAD who underwent ACC_{max} measurement(s) along with computed tomography angiography of the abdominal aorta and lower extremities (reference test) were eligible for inclusion. ACC_{max} measurements of the posterior tibial artery, anterior tibial artery and peroneal artery were collected. Diagnostic performance was assessed by using sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the curve (AUC).

Results: In total, 340 patients (618 limbs) were included. Approximately 40% suffered from DM and 30% had CKD. Diagnostic performance of the ACC_{max} to detect PAD for the posterior tibial artery showed a sensitivity of 90%, specificity of 93%, positive likelihood ratio of 12.83, and negative likelihood ratio of 0.11 (AUC, 0.953). For the anterior tibial artery, these results were 94%, 97%, 32.06, and 0.06 (same sequence as presented before) with an AUC of 0.984. The peroneal artery had a performance of 86%, 89%, 7.51, and 0.16, respectively (AUC, 0.893). Diagnostic accuracy of the ACC_{max} did not diminish in subgroup analysis for patients with DM or CKD.

Conclusions: The ACC_{max} showed excellent diagnostic performance to detect PAD, independent of patients prone to medial arterial calcification. (J Vasc Surg 2024;79:405-11.)

Keywords: Peripheral artery disease; Lower extremity artery disease; Diagnostics; Point of care testing; Ultrasound imaging; Doppler; Systolic acceleration

Peripheral artery disease (PAD) is a common disorder, affecting approximately 237 million people worldwide.[1] Currently, the ankle-brachial index (ABI) is considered the first-line test for screening and diagnosing PAD. According to current guidelines, an ABI of ≤0.90 is set as the threshold to define PAD, with a corresponding sensitivity and specificity of 75% and 86%.[2,3] This indicates that the test can quite reasonably confirm PAD, but fails to rule out, disease. For example, in a population with a 50% prevalence of PAD, almost one-quarter of patients (22.5%) is missed in case of a negative ABI (ie, >0.90). Its sensitivity diminishes even further in patients with diabetes mellitus (DM) or end-stage chronic kidney disease (CKD) owing to medial arterial calcification, leading to falsely elevated ABI measurements.[4-6] Guidelines advise that alternative tests such as toe pressure, toe-brachial index (toe-brachial index), or Doppler waveform analysis should be performed in case of incompressible ankle arteries or an ABI of >1.40.[3,7] However, similar to the ABI, the reliability of these tests is low and cannot mitigate false normal results.[4]

It is expected that the number of patients with DM will increase to nearly 370 million people by 2030 worldwide. Eventually, one out of four of these patients may suffer from a diabetic foot ulcer during their life.[8] Roughly 50% to 65% of these patients have underlying PAD, which is a strong predictor for nonhealing foot ulcers and has major consequences on clinical outcome.[9-11] In these patients, urgent revascularization is required for limb salvage. Also prompt initiation of cardiovascular risk management is necessary to decrease cardiovascular complications.[7] It is, therefore, of the utmost importance that diagnostic tests to identify PAD are easily obtained, accurate and preferably noninvasive (ie, bedside).

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Because currently used diagnostic tests are insufficient in this patient group, improvement in point-of-care testing to detect PAD is crucial.

The maximal systolic acceleration (ACC_{max}) is a promising and relatively new noninvasive parameter measured by Doppler ultrasound examination. One of the significant benefit of the ACC_{max} is that it does not require external compression, making its diagnostic performance theoretically less susceptible to incompressible arteries. A previous in vitro study has demonstrated a strong correlation between ACC_{max} and intra-arterial pressure gradient, and an in vivo study has even shown superior performance of the ACC_{max} compared with conventional noninvasive pressure measurements (eg, ABI and TBI) in healthy volunteers.[12,13] However, further assessment in patients is necessary to determine its clinical value.

The main objective of this study was to evaluate the diagnostic performance of the ACC_{max} to detect PAD in patients referred to the hospital. Secondary objectives included the diagnostic reliability in patients who are prone to medial arterial calcification (ie, DM and CKD) and an analysis of the distribution pattern of the ACC_{max} in relation to severity of symptoms.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Diagnostic performance of the Doppler-derived maximal systolic acceleration to detect peripheral arterial disease showed a sensitivity and specificity of >90% in 618 studied limbs. Diagnostic accuracy did not diminish in subgroup analysis for patients with diabetes mellitus or chronic kidney disease.
- **Take Home Message:** The maximal systolic acceleration is a new, noninvasive parameter that exhibits excellent diagnostic performance to diagnose and exclude PAD. Therefore, this point-of-care test holds significant promise as a screening tool, particularly in patients with diabetes mellitus or chronic kidney disease.

METHODS

Study design. This retrospective diagnostic accuracy study was conducted at the Leiden University Medical Centre, a Dutch tertiary referral hospital. Ethical approval was obtained from the Research and Science Committee of the surgery division (2022-047) and granted on September 7, 2022. Patients ≥18 years old who had suspected PAD and underwent ACC_{max} measurement(s) along with computed tomography angiography (CTA) of the abdominal aorta and lower extremities were analyzed. ACC_{max} measurements were blinded to the reference test because patients were only included if the ACC_{max} test was done before CTA. CTA was assessed by experienced vascular radiologists. The maximum duration between both diagnostic tests was 6 months, without intermediate (endo)vascular interventions. Because CTA always examines both limbs, the contralateral side was included as well in case the ACC_{max} was measured. Patients in whom the CTA could not reliably be assessed owing to extensive crural calcifications were excluded.

Peripheral arterial disease (PAD) was defined as >50% stenosis on CTA, consistent with previous studies regarding PAD.[4-6] Although digital subtraction angiography is still regarded as the gold standard to diagnose PAD, CTA has been accepted as reliable reference test as well.[14] To reliably assess diagnostic performance, arterial pathways were defined for each crural vessel separately, which included the posterior tibial artery (PTA), anterior tibial artery (ATA), and the peroneal artery. The arterial pathway was defined as all segments proximal to the designated artery. All arterial pathways included the distal abdominal aorta, iliac artery, common femoral artery, superficial femoral artery, and popliteal artery. For the posterior tibial and peroneal arteries, the tibioperoneal trunk was added. All designated arteries were included in their own arterial pathway as well.

Data were extracted by using CTcue and included patient information from January 1, 2008, to December 31, 2022. Next to diagnostic test results, demographic information such as age, sex, comorbidities (DM, CKD with and estimated glomerular filtration rate of <60 mL/min/1.73 m^2, hypertension, hypercholesterolemia, cardiac disease, kidney transplantation, and smoking) and Fontaine classification were obtained from electronic patient files. Two researchers (SW and SD) extracted the data and constructed the database.

ACC_{max}. The ACC_{max} is a velocimetric Doppler-derived parameter that is measured in the systolic phase of an arterial flow (expressed in m/s^2). As previously described by Brouwers et al,[13] this parameter is measured by Doppler ultrasound and calculated at the maximal slope of the upstroke. A tangent line can be made manually by adding two points exactly following this maximal slope (Fig 1). The acceleration of the tangent line is automatically calculated in m/s^2 (ACC_{max}). In general, a steeper curve represents a better hemodynamic profile of the artery. Previous studies showed a high interobserver agreement for ACC_{max} measurements (intraclass coefficient, 0.97-0.99) in an experimental setting.[12,13] All measurements of the crural vessels were performed near the ankle region and no period of rest or exercise before testing was applied. One measurement takes approximately 30 to 60 seconds. An Acuson S2000 System (Siemens Medical Solutions, Ultrasound Division, Issaquah, WA) equipped with a 9L4 9-4 MHz linear

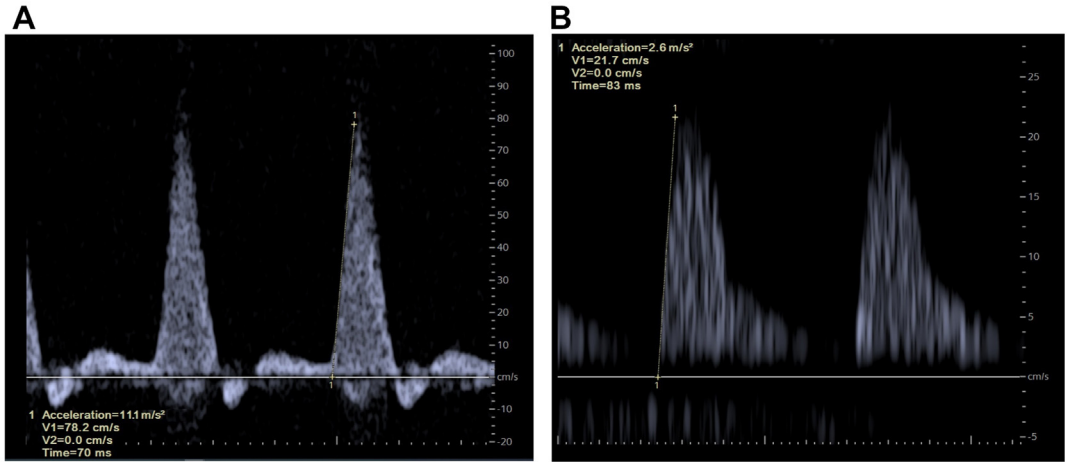

Fig 1. Doppler ultrasound examination. **(A)** Normal triphasic waveform showing a maximal systolic acceleration (ACC_{max}) measurement of 11.2 m/s^2, calculated at the maximal slope in the systolic phase of an arterial flow (tangent line indicated by 1). **(B)** Abnormal waveform showing an ACC_{max} measurement of 2.6 m/s^2, calculated at the maximal slope in the systolic phase of an arterial flow (tangent line indicated by 1). Note the differences in scales between the figures.

transducer was used during the entire study period. The scale (velocity and time) and sweep were optimized for each examination. The velocity scale was set slightly higher than the peak systolic velocity (Doppler waveform covering at least three-quarters of the window is necessary). The time scale contained a maximum of three to four heartbeats. In case dysrhythmias were present, the most representative waveform for that particular patient was used. No additional software is required to obtain the ACC_{max}.

Statistical analysis. Descriptive statistics were calculated for participant demographics using means for continuous variables and proportions for categorical variables. Diagnostic accuracy was measured by calculating sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR). PLR and NLR are derivatives of sensitivity and specificity, and represent the effect on post-test probability of disease. The ratios were categorized as follows: no effect (PLR, 1; NLR, 1), small effect (PLR, 2-5; NLR, 0.2-0.5), moderate effect (PLR, 5-10; NLR, 0.1-0.2), or large effect (PLR, >10; NLR, <0.1).[15] Analyses were made for each artery separately. Subanalyses were conducted for patients with DM and CKD.

The Youden's index was used to determine optimal cutoff values of the ACC_{max} to diagnose PAD for each artery. Additionally, diagnostic performance was calculated for all cutoff values from 3 to 8. Receiver operating characteristic curve analyses were performed to estimate the area under the curve (AUC) with 95% confidence intervals (CIs). Box plots were used to demonstrate the distribution of ACC_{max} for different patient groups with median and interquartile ranges (IQRs). These groups were classified as asymptomatic limbs without stenosis, claudication and patients with chronic limb-threatening ischemia (CLTI). To representatively simulate the clinical condition of a patient, the highest ACC_{max} measurement of the ATA and PTA was taken. The Mann-Whitney *U* test was used to investigate differences between these categorical groups. A *P* value of <.05 was considered statistically significant. Calculations were executed in SPSS for Windows version 25.0 (IBM, Armonk, NY).

RESULTS

In total, 600 patients were screened for eligibility, of which 359 could be included after the first screening. Owing to extensive calcifications on CTA, 19 patients had to be excluded. Eventually, 340 patients (618 limbs) were included in this study. Table I provides an overview of patient characteristics. The mean age of patients was 68 years and the majority was male (61%). Comorbidities were frequently present, in particular DM (40%), CKD (30%), and cardiac disease (52%). The majority of patients had claudication symptoms (40%) or CLTI (37%). The mean duration between ACC_{max} and CTA was 20 days.

Diagnostic performance. The diagnostic accuracy of the ACC_{max} to diagnose PAD according to highest Youden index is presented in Table II. The optimal cutoff value was between 5 and 6 m/s^2 for all three crural arteries. The PTA had a sensitivity of 90%, specificity of 93%, PLR of 12.83, and NLR of 0.11 when using a cutoff value of 5.55 m/s^2. For the ATA, these results were 94%, 97%, 32.06, and 0.06 (same sequence as presented before), with a cutoff value of 5.15 m/s^2. The peroneal artery showed a performance of 86%, 89%, 7.51. and 0.16, respectively, applying a cutoff value of 5.00 m/s^2.

Fig 2 displays the receiver operating characteristic curves for each artery separately. The AUC of the PTA

Table I. Patient characteristics

Variable	No. (%)
Total patients and limbs	340-618 (100)
Sex	
Male	206 (60.6)
Female	134 (39.4)
Side	
Right limb	312 (50.5)
Left limb	306 (49.5)
Age, years, mean ± SD	67.7 ± 11.2
Age range, years	35-93
Comorbidities	
DM	135 (39.7)
CKD (eGFR <60 mL/min/1.73 m^2)	101 (29.7)
Cardiac disease	175 (51.5)
Hypertension	243 (71.5)
Hypercholesterolemia	220 (64.7)
Kidney transplantation	24 (7.1)
History of smoking	227 (66.8)
Postintervention in medical history	
Yes (PTA, stent, bypass, EVAR)	166 (26.9)
Fontaine classification	
Fontaine IIa	88 (14.2)
Fontaine IIb	157 (25.4)
Fontaine III	83 (13.4)
Fontaine IV	143 (23.1)
Asymptomatic	113 (18.3)
Unknown	34 (5.5)
PAD prevalence (stenosis on CTA >50%)	530 (85.8)

CKD, Chronic kidney disease; *CTA*, computed tomography angiography; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration rate; *EVAR*, endovascular aortic repair; *PAD*, peripheral arterial disease; *PTA*, percutaneous transluminal angioplasty; *SD*, standard deviation.

was 0.953 with a 95% CI of 0.93 to 0.98. The AUC measurement of the ATA was 0.984 (95% CI, 0.97-1.00) and AUC of the peroneal artery was 0.893 (95% CI, 0.83-0.96).

The diagnostic performances of each artery separately for different cutoff values (from 3 to 8) are depicted in Table III. In general, a higher cutoff value established a higher sensitivity and better NLR. A lower cutoff value resulted in a higher specificity and better PLR.

Diagnostic accuracy in DM and CKD. Table II provides an overview of ACC_{max} performance per artery in subgroup analyses for patients with DM and CKD. The diagnostic accuracy of the ACC_{max} for these subgroups did not deteriorate as compared with the overall study population.

ACC_{max} distribution. Fig 3 shows the box plot of ACC_{max} measurements in relation to severity of symptoms. Median acceleration of asymptomatic patients without PAD was 10.6 (IQR, 10.1-11.5), 2.50 (IQR, 1.00-5.00) for claudication patients, and 0.80 (IQR, 0.20-2.25) for patients with CLTI. Significant differences ($P = .001$) of ACC_{max} measurements were seen between these groups.

DISCUSSION

The results of this study confirm that the ACC_{max} has the potential to be valuable in the diagnostic workup of PAD. Excellent diagnostic performance was demonstrated with a sensitivity and specificity of >90% for the PTA and ATA, while not being influenced by the presence of DM or CKD. These results are in line with previous in vitro and in vivo studies on the ACC_{max}.[12,13] Furthermore, the sample size of this study was much larger when comparing it with previous diagnostic research for PAD.[4-6]

Our data suggest that the ACC_{max} is highly accurate in detecting and excluding PAD. As part of the diagnostic workup, we recommend measuring this bedside test for the ATA and PTA, in which we found excellent AUC above 0.95. In comparison with previous ABI findings, our results suggest an improvement in sensitivity. Specifically, we observed sensitivity rates of 94% for the ATA and 90% for the PTA, along with corresponding NLRs of 0.06 and 0.11, respectively. In a clinical setting, this result could indicate that the ACC_{max} is able to rule out PAD. As previously mentioned, current ABI methods miss approximately one-fourth of patients. Based on our findings, the ACC_{max} could decrease this number to 1 in 10 patients. This test could represent a significant improvement in diagnostic strategies for individuals with a suspicion of PAD.

In addition, diagnostic performance for patients who were prone for medial arterial calcification (MAC) (ie, DM and CKD) were investigated. This factor is of great importance, because currently used diagnostic tools are particularly vulnerable for falsely positive findings in this group. As mentioned, previous research showed a decrease of diagnostic performance of ABI for patients with DM (63.5% sensitivity).[6] Although TBI measurements are advised in these cases, the accuracy of these tests remains disappointing, with a sensitivity of 83.0% and a specificity of 66.3%.[3,6] Moreover, absolute toe pressure showed unreliable results for different thresholds (50, 70, and 98 mm Hg) in patients prone to MAC.[4] Our study showed that ACC_{max} performance was noninferior within these subgroups. Sensitivity and specificity analyses were comparable with the overall group. This result corresponds with our assumption that the ACC_{max} would be less influenced by the presence of MAC. The primary reason for this is that no external pressure measurement is required, as is seen in the ABI, TBI, and toe pressure. This fact is of great relevance in the diagnostic workup of patients with diabetic foot ulcers. In this patient group, prompt and reliable assessment of PAD is

Table II. Diagnostic accuracy of maximal systolic acceleration (ACC_{max}) per artery

	Cutoff value ACC_{max} according to the Youden index	AUC (95% CI)	Sensitivity % (95 CI)	Specificity % (95 CI)	PLR (95 CI)	NLR (95 CI)
PTA	**5.55**	**0.95 (0.93-0.98)**	**90 (86.5-92.5)**	**93 (86.1-97.1)**	**12.83 (6.3-26.2)**	**0.11 (0.08-0.15)**
DM	**5.55**	0.96 (0.93-0.99)	87 (80.4-91.4)	93 (78.6-99.2)	13.42 (3.5-51.4)	0.14 (0.10-0.21)
CKD	**5.55**	0.99 (0.98-1.00)	92 (86.3-96.3)	100 (85.8-100.0)	NA	0.08 (0.04-0.14)
ATA	**5.15**	**0.98 (0.97-1.00)**	**94 (90.9-96.7)**	**97 (83.3-99.9)**	**32.06 (4.7-221.1)**	**0.06 (0.04-0.10)**
DM	**5.15**	0.99 (0.98-1.00)	93 (87.5-97.1)	100 (82.4-100.0)	NA	0.07 (0.03-0.13)
CKD	**5.15**	0.99 (0.98-1.00)	96 (90.0-98.9)	100 (66.4-100.0)	NA	0.04 (0.02-0.11)
Peroneal artery	**5.00**	**0.89 (0.83-0.96)**	**86 (80.8-90.0)**	**89 (73.3-96.8)**	**7.51 (2.98-18.9)**	**0.16 (0.11-0.22)**
DM	**5.00**	0.86 (0.76-0.96)	87 (78.4-92.7)	83 (58.6-96.4)	5.20 (1.85-14.7)	0.16 (0.09-0.28)
CKD	**5.00**	0.87 (0.79-0.94)	84 (74.8-91.0)	100 (29.2-100.0)	NA	0.16 (0.10-0.26)

ATA, Anterior tibial artery; *AUC*, area under the curve; *CKD*, chronic kidney disease; *CI*, confidence interval; *DM*, diabetes mellitus; *NLR*, negative likelihood ratio; *PLR*, positive likelihood ratio; *PTA*, posterior tibial artery.

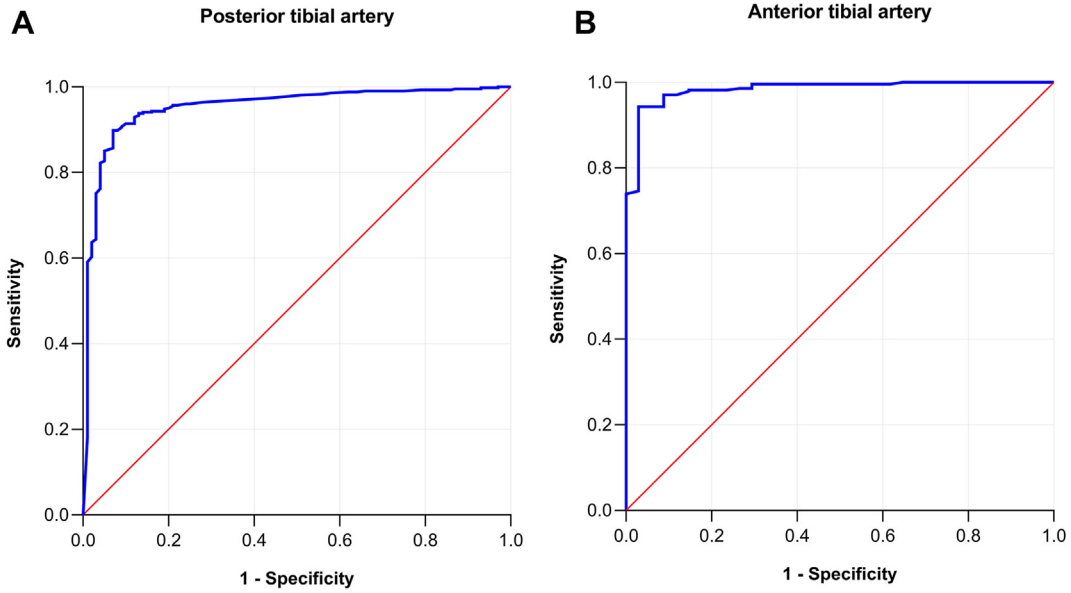

Fig 2. Receiver operating characteristics curve for maximal systolic acceleration (ACC_{max}) per artery. **(A)** Posterior tibial artery (PTA). **(B)** Anterior tibial artery (ATA). **(C)** Peroneal artery.

essential to prevent complications. Although necessary, the currently used tests (ABI, TBI, and toe pressure) fail to do so. When using the ACC_{max} as the bedside test in these patients, no decrease in diagnostic performance was observed. As shown in Table II, it is possible to accurately diagnose and rule out PAD in this challenging group of patients (DM or CKD). This provides the opportunity to directly start with cardiovascular risk management and aid in the decision for potential revascularization to restore wound healing and prevent eventual amputations.

Next to a superior diagnostic accuracy, the ACC_{max} could have some additional practical benefits compared with the ABI. First, ACC_{max} measurements can be obtained very easily. It takes <5 minutes to measure this parameter in the ATA and PTA. If abnormalities in (one of) these vessels are present, one could simply measure the ACC_{max} more proximally until normal values or the external iliac artery is reached. When using such a workup, more detailed information about the vascular system is gathered, including the probable location of the stenosis. This practice could improve efficiency and

Table III. Diagnostic accuracy of maximal systolic acceleration (ACC_{max}) for different cutoff values per artery

Cutoff values	Sensitivity (%)	Specificity (%)	PLR	NLR
PTA				
3	74	97	24.6	0.27
4	83	95	16.53	0.18
5	88	93	12.59	0.13
6	91	90	9.14	0.10
7	94	86	6.70	0.07
8	94	81	4.96	0.07
ATA				
3	81	97	27.56	0.20
4	88	97	29.99	0.12
5	94	97	31.94	0.06
6	97	91	11.01	0.03
7	98	85	6.68	0.02
8	99	71	3.35	0.02
Peroneal artery				
3	78	89	6.82	0.25
4	82	89	7.18	0.20
5	86	89	7.51	0.16
6	88	74	3.42	0.16
7	91	69	2.89	0.13
8	93	51	1.91	0.14

ATA, Anterior tibial artery; *NLR*, negative likelihood ratio; *PLR*, positive likelihood ratio; *PTA*, posterior tibial artery.

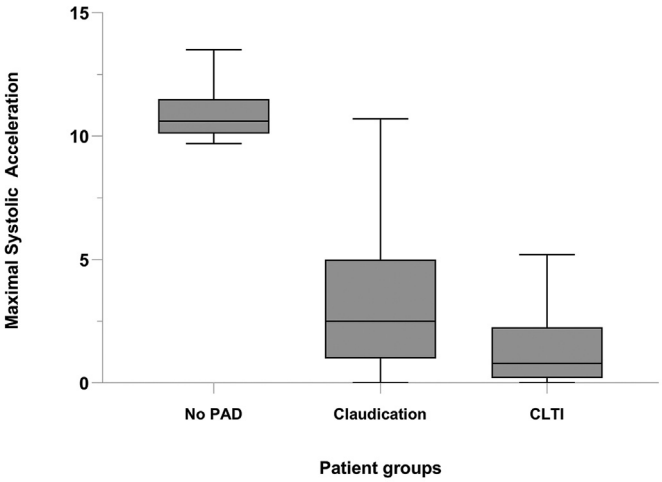

Fig 3. Box plot analysis: Maximal systolic acceleration (ACC_{max}) of the posterior tibial artery (PTA) in relation to symptoms. Group 1 = asymptomatic without peripheral arterial disease (*PAD*) (median, 10.60 m/s^2; interquartile range [IQR], 10.10-11.50; n = 45). Group 2 = claudication (median, 2.50 m/s^2; IQR, 1.00-5.00; n = 235). Group 3 = chronic limb-threatening ischemia (*CLTI*) (median, 0.80 m/s^2; IQR, 0.20-2.25; n = 201). The box contains the 25th to 75th percentiles, and the center line denotes the median value (50th percentile). The upper and lower whiskers mark the 5th and 95th percentiles. Values beyond these bounds are considered outliers.

further clinical decision-making when combined with symptoms. This promising and time-saving workup needs to be explored further to ensure its validity.

It is noteworthy that all calculated optimal cutoff values of the ACC_{max} fell between 5 and 6. Besides determining the cutoff point for the ACC_{max}, this study also assessed the diagnostic performance at different thresholds (range, 3-8). These thresholds may prove helpful in clinical decision-making because they correspond with specific diagnostic performances. For instance, by examining the results for the ATA in Table III, it is evident that an ACC_{max} of <4 almost always proves PAD (specificity, 97%; PLR, 30.0), while an ACC_{max} of >7 effectively rules out disease (sensitivity, 98%; NLR, 0.02). Our experiences suggest that these findings could be particularly useful in clinical practice.

Additionally, ACC_{max} measurements had excellent correlation with severity of disease. Asymptomatic patients without PAD had a median ACC_{max} of 10.6, whereas patients with claudication and CLTI had an ACC_{max} of 2.50 and 0.80, respectively. As can be seen in Fig 3, significant differences were found between these groups. It should be recognized that there is also overlap for claudication and CLTI patients. However, a patient with an ACC_{max} measurement of <0.50 has a very high probability of CLTI and probably requires urgent therapy to prevent complications.

Limitations. These results should be considered in the context of some limitations. First, this study had a retrospective design, which carries certain drawbacks, such as the lack of a prespecified structured system of ACC_{max} measurements. Second, because all patients underwent CTA, the overall study population had a relatively high prevalence of PAD. Although the contralateral leg was investigated as well, it would have been ideal to include a larger number of patients without PAD to achieve a lower pretest probability of disease. Last, this study used CTA as a reference standard for PAD diagnosis. Although CTA is commonly used clinically and has also been used as a reference test in previous diagnostic research, it is not considered the gold standard imaging technique.[4-6] In particular, calcified crural arteries may be difficult to assess on CTA, and these patients had to be excluded if reliable assessment was not possible. Although this only applied to 19 patients, it could potentially have led to an underestimation of the diagnostic performance of the ACC_{max}.

CONCLUSIONS

The ACC_{max} is a new, noninvasive, Doppler-derived parameter that exhibits excellent diagnostic performance to diagnose and exclude PAD. Its accuracy is not compromised in patients who are prone to MAC,

such as those with DM or CKD. Consequently, this point-of-care test holds significant promise as a screening tool for these challenging patient populations.

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AUTHOR CONTRIBUTIONS

Conception and design: SW, SD, JV, JS, AS, JH, JB
Analysis and interpretation: SW, AS, JH, JB
Data collection: SW, SD, RW
Writing the article: SW, SD, JB
Critical revision of the article: SW, SD, RW, JV, JS, AS, JH
Final approval of the article: SW, SD, RW, JV, JS, AS, JH, JB
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Overall responsibility: JB

DISCLOSURES

None.

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