Maximal systolic acceleration in atherosclerotic vascular disease

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Chapter 3

Using maximal systolic acceleration to diagnose and assess the severity of peripheral artery disease in a flow model study

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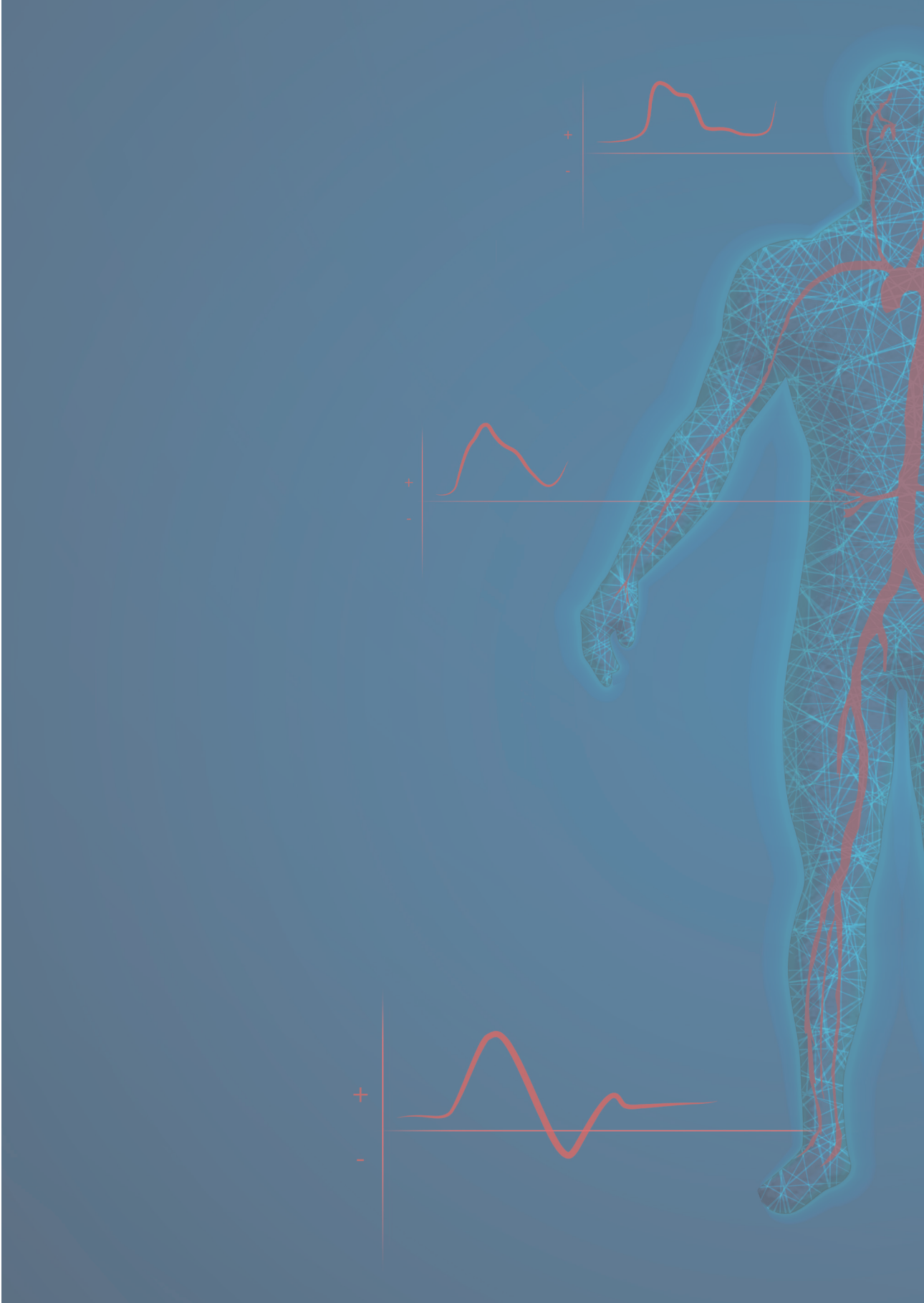

Abstract

Background

Because of the presence of medial calcific sclerosis, both ankle-branchial index and toe pressure measures can yield misleading results when attempting to diagnose peripheral artery disease (PAD). A new ultrasound parameter, maximal systolic acceleration (ACC_{max}), can be an accurate tool for diagnosing PAD, including in diabetic patients. However, it has not been evaluated thoroughly. The aim of this study was to assess the feasibility of using ACC_{max} to diagnose and assess the severity of PAD.

Methods

The human circulatory system was simulated using an in vitro circulatory system driven by a pulsatile pneumatic pump. Arterial stenosis of various degrees (50%, 70%, 80%, and 90%) was simulated in order to investigate the change in several ultrasound parameters (including ACC_{max}), as well as the intraluminal mean arterial pressure gradient. In a separate set of measurements, interobserver variability was measured using two investigators who were unaware of the degree of stenosis.

Results

ACC_{max} significantly decreased ($P < .001$), and the pressure gradient increased ($P < .001$) as the degree of stenosis increased. Moreover, we found a strong correlation between ACC_{max} and the pressure gradient ($R^2 = 0.937$). Finally, interobserver variability with respect to ACC_{max} was extremely low, with an intraclass correlation coefficient of 0.99.

Conclusions

The results of this flow model study suggest that ACC_{max} can be a valid, noninvasive tool for diagnosing PAD. Moreover, our finding that ACC_{max} decreases as the severity of stenosis increases, together with the strong correlation between ACC_{max} and the pressure gradient, suggests that ACC_{max} may be useful as an alternative diagnostic tool for assessing the severity of PAD. These promising in vitro data warrant further study in a clinical setting.

Clinical Relevance

Limb pressure measurements and the determination of pressure index values (ankle-branchial index and toe pressure) are commonly used in patients with symptoms consistent with peripheral arterial disease. However, ankle-branchial index and toe pressure can be falsely elevated or falsely normal due to medial calcific sclerosis. In this in vitro flow-model study, the maximal systolic acceleration (ACC_{max}) significantly decreased as the degree of stenosis increased. Furthermore, there was a strong correlation between ACC_{max} and the intraluminal pressure gradient. These results suggest ACC_{max} may provide a robust noninvasive technique for assessing the severity of peripheral arterial disease.

Introduction

Several noninvasive tools are currently used for diagnosing and assessing the severity of atherosclerotic peripheral artery disease (PAD): ankle-branchial index (ABI), toe-brachial index (TBI), toe pressure (TP), and pulse volume recording.[1,2] Although an ABI value of <0.90 is considered a diagnostic criteria for PAD in patients with claudication,[3,4] the results of this test can be misleading as a result of vessel stiffness caused by medial calcific sclerosis, possibly leading to either a falsely high or falsely normal ankle pressure.[5] However, both TBI and TP are generally considered to be more reliable indicators of PAD severity in patients with incompressible crural and/or pedal arteries.[6] Yet, both TBI and TP can provide falsely elevated values as a result of incompressible digital arteries, and both tests are dependent on temperature.[7,8,9] Incompressible arteries occur primarily in patients with a long history of diabetes, advanced age, and/or end-stage renal disease. Compared to patients without diabetes, those with diabetes have a fourfold higher risk of developing PAD,[10] and 65% of patients with a diabetic foot ulcer also develop ischemic complications.[6,11] Furthermore, approximately 20% of patients with critical limb ischemia (CLI) have incompressible vessels due to artery calcification. Finally, the waveform morphology measured using pulse volume recording is relatively insensitive for diagnosing CLI.[12] Thus, determining the severity of PAD using currently available noninvasive measurements can be challenging, particularly in patients with CLI and/or diabetes.

A new noninvasive approach that is particularly promising for detecting and quantifying PAD is duplex-derived maximal systolic acceleration (ACC_{max}). Van Tongeren et al[13] and Buschmann et al[14] showed the accurate diagnostic properties of ACC_{max}, also in diabetic patients. Although ACC_{max} has already been used to detect renal artery stenosis,[15,16,17,18] to our knowledge, it has not been evaluated thoroughly for PAD. We think that if you want to introduce a new parameter to diagnose PAD, you must start from basic principles. Apart from complex clinical settings that occur in reality (eg, impact from cardiac output, shear rate, collateral circulation, vascular compliance, outflow obstruction), this in vitro flow model study investigated the impact of different artificial stenosis and compared ultrasound parameters with the intraluminal pressure gradient. From here, further structured substantiation of the ACC_{max} and its clinical value need to be determined.

Methods

In vitro circulatory system

Our in vitro circulatory system was previously validated with respect to simulating the human circulatory system.[19,20,21,22] Fig 1 shows a systematic representation of the in vitro circulatory system, which consists of a pneumatically driven pulsatile pump, a ball valve, a compliance air chamber, an arterial stenosis model (a removable tube for inserting the stenosis), a pressure band to simulate peripheral resistance, and a collateral system with intrinsic peripheral resistance. The following degrees of stenosis were used at two different lengths (2 and 8 cm): 50%, 70%, 80%, and 90%; these stenosis models were easily switched in the arterial stenosis model. Collateral peripheral resistance (Fig 1; F_{col}) was necessary in order to maintain consistent prestenotic mean arterial pressure (MAP) with the various setups. To investigate the correlation between Doppler ultrasound parameters with the degree of stenosis and intra-arterial pressure gradient, the other variables of the in vitro circulatory system, with regard to the peripheral resistance (distal to the stenosis; Fig 1, *F*), compliance, shear rate, and cardiac output, were unchanged during the different test setups. In addition, the pneumatically driven pulsatile pump settings used for the in vitro

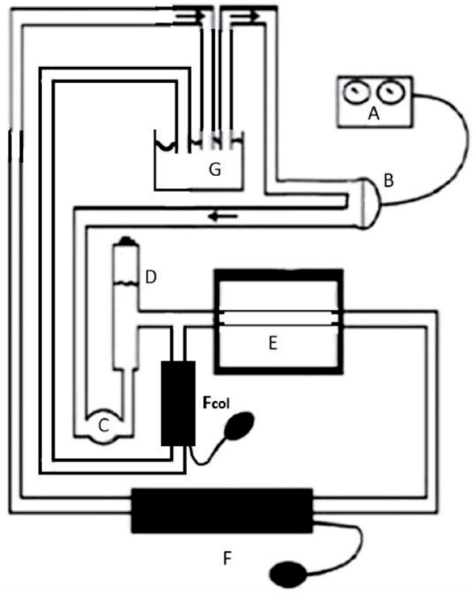

Fig 1: Schematic illustration depicting in vitro circulatory system used in this study. In vitro circulatory system was composed of (A) pneumatically driven pulsatile pump, (B) simulated left ventricle, (C) ball valve, (D) compliance air chamber, (E) arterial stenosis model, (F) pressure band to simulate peripheral resistance, (Fcol) collateral system with intrinsic peripheral resistance, and (G) open reservoir.

circulatory system were unchanged throughout the various measurements. The Doppler ultrasound parameters were measured 30 cm from the stenosis. To simulate human blood, a starch solution with the same viscosity as human blood was used.[19,21,22] SonoVue (Bracco Imaging Europe, Amsterdam, the Netherlands) was used to optimize the Doppler imaging wave.[23] Intraluminal prestenotic and poststenotic MAP was measured using a RadiAnalyzer Xpress device equipped with a PressureWire (St Jude Medical, St Paul, MN).

Test setups

Fig 2 shows an overview of the various setups used in this study. In setup 1, no stenosis is included. Setups 2 through 5 have various degrees of stenosis (2 cm). Setups 6 through 9 have various degrees of stenosis (8 cm). Finally, setups 10 through 13 have three 2-cm stenoses in series.

Degree of stenosis

In this study, each stenosis was concentric with the vessel, and the degree of stenosis was based on the reduction in the vessel's diameter. It is important to note that a reduction in

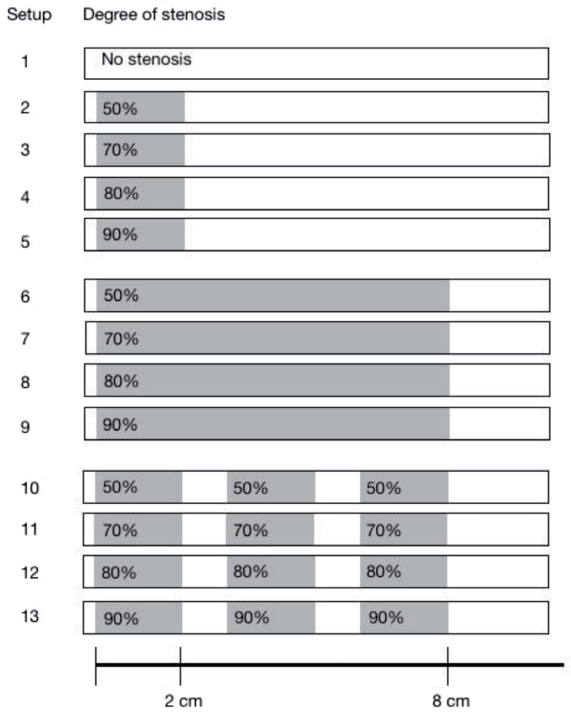

Fig 2: Schematic overview of various study setups. In setups 2 through 13, each stenosis (either 2 or 8 cm) is indicated in gray, with corresponding degree indicated as percentage.

diameter does not correlate with the same reduction in the cross-sectional area; for example, a 50% reduction in diameter corresponds to a 75% reduction in area.[24] Table I provides a summary of the stenoses used in this study and their corresponding reductions in diameter and area.

Degree of stenosis in diameter reduction	Diameter of stenosis, mm	Degree of stenosis in area reduction	Area of stenosis, mm^2
0	12.1	0	115.0
50%	6.1	75%	28.7
70%	3.6	91%	10.3
80%	2.4	96%	4.6
90%	1.2	99%	1.1

Table 1: Degree of stenosis and corresponding reduction in diameter and area of various stenoses

Doppler ultrasound

All Doppler ultrasound procedures were performed by the same vascular ultrasound specialist, who used an Acuson S2000 System, Helix Evolution (Siemens Medical Solutions, Ultrasound Division, Issaquah, Wash) equipped with a 9L4 9-4 MHz linear transducer. All measurements were performed with a fixed 60-degree angle of insonation. ACC_{max} was calculated by computer at a single representative curve as described by van Tongeren et al[13] and is expressed in meters per second. It is important to note that the ACC_{max} occurs at the maximal slope in the systolic phase (Fig 3). ACC_{max} was measured distal to the stenosis, so there is no interference from medial calcific sclerosis. ACC_{max} should not be confused with either acceleration time (AT) or mean systolic acceleration (ACC_{sys}).

Interobserver variability

In a separate set of measurements, interobserver variability of ACC_{max} was calculated using measurements obtained by two investigators who were unaware of the degree of stenosis. In this subset, only a single stenosis (50%, 70%, 80%, 90%, or no stenosis) was used in each experiment. For each degree of stenosis, ACC_{max} was measured five times by each investigator.

Distance between stenosis and measurement point

To examine the effect of the distance between the stenosis and ACC_{max}, ACC_{max} was measured at a distance of 30 and 20 cm from the stenosis in a test setup with an 80% stenosis and without stenosis.

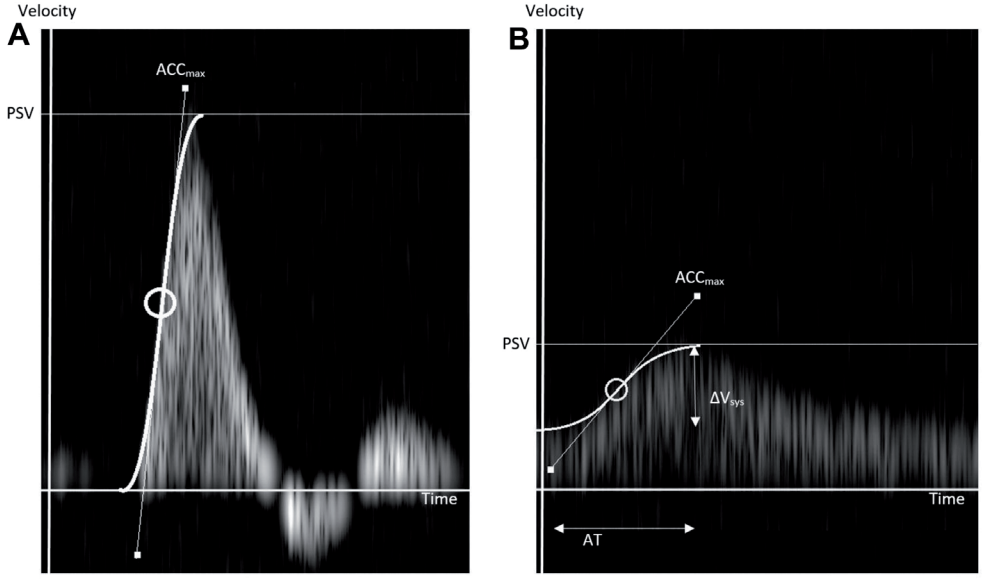

Fig 3: Example analysis of Doppler spectrum. A, Normal triphasic Doppler waveform. Maximal systolic acceleration (*ACCmax*) is measured at inflection point at which upstroke changes from concave up to concave down. It is equal to slope of tangent line on curve at inflection point. B, Example of abnormal monophasic Doppler waveform. ACC_{max}, peak systolic velocity (*PSV*), acceleration time (*AT*), and systolic velocity gradient (ΔV_{sys}) are shown. ACC_{max} is measured at visually judged maximum derivative of systolic phase. ACC_{max} should not be confused with mean systolic acceleration (ACC_{sys}), which is slope between beginning of systolic upstroke and peak of systole and is calculated using following equation: $ACC_{sys} = \Delta V_{sys}/AT$.

Statistical analysis

All analyses were conducted by SPSS Statistics 23.0 software (IBM, Armonk, NY). Linear regression was used to relate ACC_{max} to other ultrasound parameters and degree of stenosis. Differences with $P < .05$ were considered statistically significant. Using a linear regression model, a coefficient of determination (R^2) was used to determine the putative association between ultrasound parameters and the intraluminal MAP gradient. Interobserver variability was measured by calculating the intraclass correlation coefficient (ICC; two-way mixed, absolute agreement), which is a measure used to determine the consistency of repeated measures. Two separate investigators measured ACC_{max} with various degrees of stenosis; an ICC value of >0.9 indicates excellent agreement between the two investigators. An independent Student *t* test was used to investigate the effect of whether ACC_{max} was affected by the distance between the stenosis and the measurement points.

Results

In vitro circulatory system

In our in vitro circulatory system, intraluminal MAP was 90 mm Hg, and ACC_{max} was 9.17 m/s^2 without a stenosis (setup 1). With different setups, prestenotic pressure was consistent and ranged from 89 to 92 mm Hg.

ACC_{max} at various degrees of stenosis

Table II summarizes the measurements obtained with each setup. With increasing degrees of stenosis, ACC_{max} significantly decreased ($P < .001$) and the intraluminal pressure gradient significantly increased ($P < .001$).

Our analysis revealed a high coefficient of determination ($R^2 = 0.937$) for the association between ACC_{max} and the pressure gradient over all 13 setups. Table III summarizes the *P* values for the ultrasound parameters between the degree in stenosis and the association with the intraluminal pressure gradient. Overall, a high pressure gradient corresponded to a low ACC_{max} value (Fig 4).

Setup No.	Degree of stenosis, %	Length of stenosis, cm	$ACC_{max,}$ m/s^2	AT, seconds	$ACC_{sys,}$ m/s^2	PSV, cm/s	Pressure gradient, mm Hg
1	0	0	9.17	0.26	6.53	188	0
2	50	2	6.33	0.26	5.24	196	27
3	70	2	1.72	0.22	1.3	65	50
4	80	2	0.99	0.19	0.71	42	62
5	90	2	0.37	0.14	0.33	20	78
6	50	8	5.01	0.27	5.21	171	35
7	70	8	1.41	0.24	1.25	23	57
8	80	8	0.83	0.18	0.67	30	68
9	90	8	0.32	0.12	0.29	15	81
10	50	3 × 2	4.96	0.24	3.46	135	42
11	70	3 × 2	1.38	0.21	1.24	58	66
12	80	3 × 2	0.44	0.17	0.41	25	71
13	90	3 × 2	0.13	0.19	0.12	12	83

Table 2: Summary of ultrasound parameters and intraluminal mean arterial pressure gradients
ACC_{max}, Maximal systolic acceleration; *ACC_{sys}*, mean systolic acceleration; *AT,* acceleration time; *PSV,* peak systolic velocity.

Ultrasound parameter	*P* value between degrees of stenosis	R^2 with pressure gradient
ACC_{max}, m/s²	<.001	0.937
AT, seconds	.031	0.696
ACC_{sys}, m/s²	<.001	0.904
PSV, cm/s	.001	0.845

Table 3: Summary of analysis of various ultrasound parameters between different test setups
ACC_{max}, Maximal systolic acceleration; ACC_{sys}, mean systolic acceleration; *AT,* acceleration time; *PSV,* peak systolic velocity.
P values are provided for association of ultrasound parameter between different degrees of stenosis; there is a significance difference in ACC_{max} ($P < .001$) between different degree of stenosis: no stenosis (test setup 1), 50% (test setup 2, 6, and 10), 70% (test setup 3, 7, and 11), 80% (test setup 4, 8, and 12), and 90% (test setup 5, 9, and 13). Coefficients of determination (R^2) between each ultrasound parameter and pressure gradient (over all test setups) are shown.

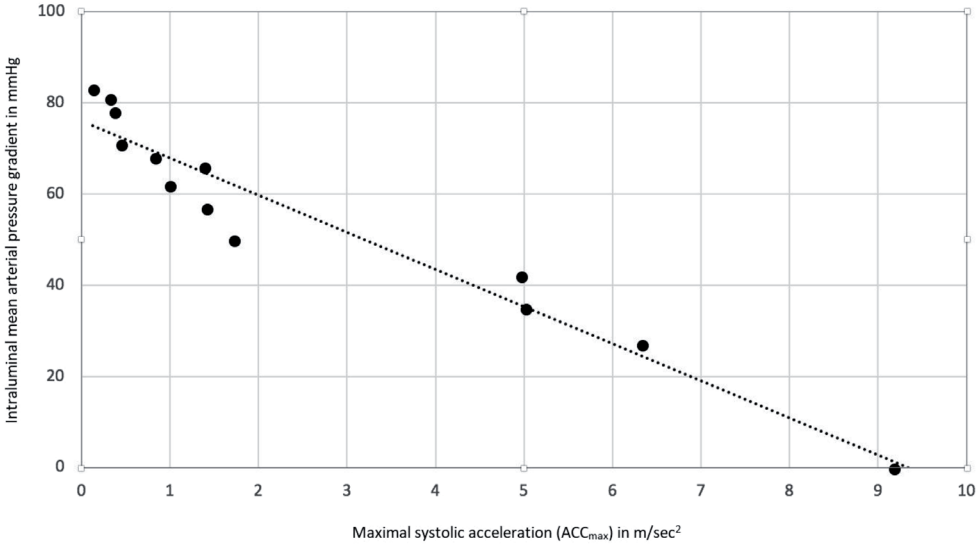

Fig 4: Intraluminal mean arterial pressure plotted against maximal systolic acceleration (*ACCmax*); coefficient of determination (R^2) was 0.937, showing high correlation. Regression line added.

In Fig 5, we plotted ACC_{max} and the intraluminal pressure gradient against the various degrees of stenosis and setups. With respect to both ACC_{max} and the pressure gradient, the setup with three 2-cm stenoses (setup 13; Fig 2) had the highest impact, and each 8-cm stenosis had a higher impact compared to the corresponding 2-cm stenosis. However, no significant differences in ACC_{max} and pressure gradient were found between 2-cm, 8-cm, and three 2-cm stenoses.

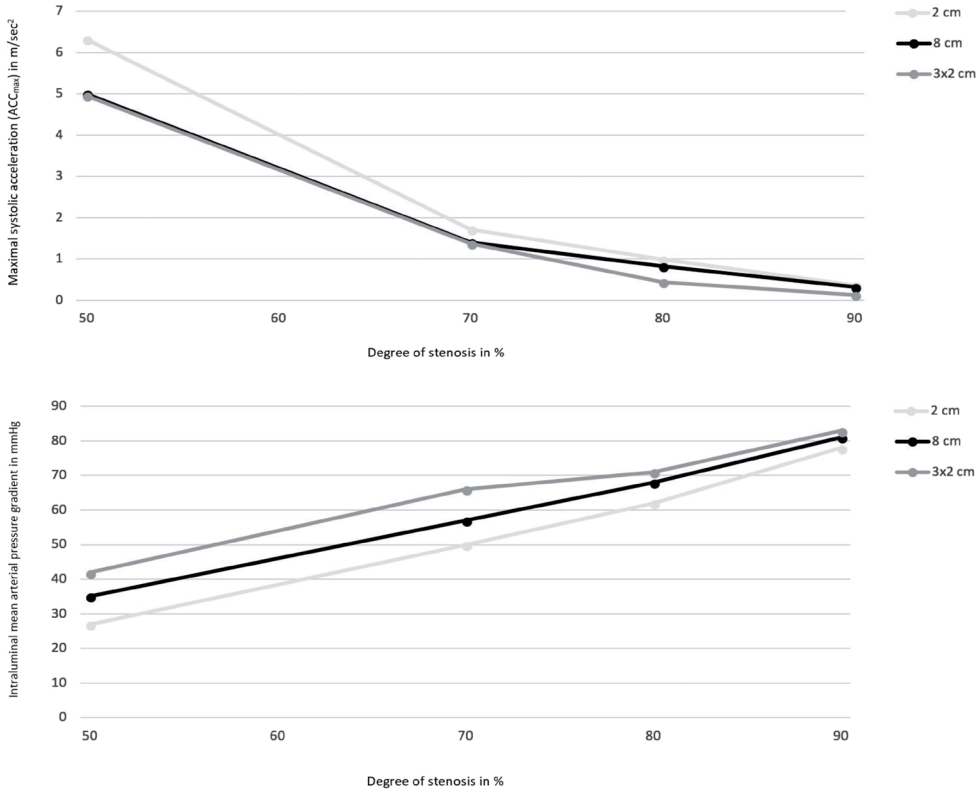

Fig 5: Maximal systolic acceleration (*ACCmax*; *top*) and intraluminal pressure gradient (*bottom*) are plotted against various degrees of stenosis based on reduction in diameter.

Interobserver variability

Two separate investigators who were unaware of the degree of stenosis measured ACC_{max}. Our analysis revealed that the ICC was 0.99 between the two investigators with respect to measuring ACC_{max} at various degrees of stenosis.

Distance between stenosis and measurement point

Finally, to examine whether ACC_{max} was affected by the distance between the stenosis and the measurement point, we measured ACC_{max} at 30 cm and 20 cm from the point of 80% stenosis and in setup 1 (Fig 2; ie, without stenosis). We found no significant differences in ACC_{max} between a distance of 30 cm and a distance of 20 cm with 80% stenosis ($P = .26$) and between the same two distances without stenosis ($P = .66$).

Discussion

ACC_{max} can be measured accurately with low interobserver variability in an experimental in vitro flow model. Importantly, ACC_{max} decreased and the pressure gradient increased as the degree of the stenosis increased. ACC_{max}, ACC_{sys}, and peak systolic velocity were significantly different between the degrees of stenosis. Furthermore, ACC_{max} had the best coefficient of determination (R^2) to intraluminal pressure gradient (Table III). Therefore, it is possible to predict the degree of stenosis with ACC_{max}, and the use of a validated ACC_{max} measurement is a potentially suitable tool for diagnosing and assessing the severity of stenosis.

Results obtained using other noninvasive measurements for diagnosing PAD—including the ABI, TBI, and TP—can be either falsely elevated or falsely normal as a result of incompressible crural, pedal, and/or digital arteries[5,7,8]; this is particularly true for patients with a long history of diabetes, advanced age, and/or end-stage renal disease.[6] Van Tongeren et al[13] previously reported that ACC_{max} can serve as an accurate marker of PAD, regardless of the presence of diabetes (36 of 73 diabetic patients had ABI ≥ 1.30). A high ACC_{max} value (>10 m/s^2) can serve to exclude the presence of PAD, whereas an ACC_{max} value of <6.5 m/s^2 is strongly indicative of PAD. In addition, Buschmann et al[14] investigated ACC_{max} and showed a better ACC_{max} area under the curve for diagnosing PAD (defined as >50% diameter reduction on angiography) compared to ABI and relative pulse slope index in patients with and without diabetes. The sensitivity of ACC_{max} was superior to that of ABI in the overall sample. The specificity of ACC_{max} was similar to that of ABI in the overall sample and was superior in diabetic patients. Moreover, we measured ACC_{max} at a position distal to the stenosis, thereby avoiding any effects associated with medial calcific sclerosis. Thus, ACC_{max} has added value compared to currently available noninvasive diagnostic tests.

Young and Tsai[25] developed a formula for calculating pulsatile blood flow by combining pressure gradient, acceleration, and degree of stenosis, which reflect the effects of viscosity, turbulence, and inertia, respectively. As the degree of stenosis increases, the turbulence index becomes the dominant factor, as this value is calculated using the square of the degree of stenosis. As a result, the inertia index, which reflects acceleration (dU/dt), decreases as the degree of stenosis—and consequently the pressure gradient—increases. Thus, it can be concluded that acceleration tends to decrease as the degree of stenosis increases.[25] Furthermore, the length of a stenosis primarily affects energy loss. The effect of a change in length is less than the effect of a change in diameter. Because entrance and exit effects contribute a large portion of the resistance offered by a stenosis, doubling the length of a lesion has less impact than two separate lesions of equal length and diameter.[26] This correlates with our findings; with respect to both ACC_{max} and the pressure gradient, the setup with three 2-cm stenoses had the highest impact, and each 8-cm stenosis had a higher

impact compared to the corresponding 2-cm stenosis (Fig 5). However, the differences in ACC_{max} and pressure gradient were both not statistically significant between these groups.

Tehan et al[10] reported that both ABI and TBI have low accuracy with respect to diagnosing PAD in diabetic patients, with sensitivity values of only 45% and 64%, respectively. In another study, the same group investigated the accuracy of using TP to diagnose PAD and found that the receiver operating curve had an area under the curve of 0.76.[27] The authors found that the sensitivity and specificity of using TP to detect PAD in diabetic patients was approximately 74% and 72%, respectively; this was similar to their control nondiabetic group, which had a sensitivity and specificity of 67% and 71%, respectively. In addition, Sawka and Carter[9] previously reported that TP is dependent on temperature.

The reproducibility of ABI has been investigated in several studies, and the measurements varied by 9% to 21%.[28,29,30,31] De Graaff et al[31] found that the interobserver ICC for ABI was 0.92 and 0.87 when measured on the same day and 1 week later, respectively; similarly, the ICC for TP was 0.88 and 0.85, respectively. In addition, they found a 1-week interobserver repeatability coefficient of 27 and 41 mm Hg for ABI and TP, respectively. In our flow model study, we found an ICC value of 0.99 between two investigators who measured ACC_{max} at various degrees of stenosis. In addition, we found no significant difference in ACC_{max} when the distance from the stenosis was 30 or 20 cm, suggesting that ACC_{max} does not depend on the distance between the stenosis and the measurement point.

Previous research[13,15,16,17,18] and our study both show that ACC_{max} is a feasible noninvasive technique for assessing the severity of PAD and renal artery stenosis. In contrast, other duplex parameters are limited to identify the severity of a PAD (particularly at multilevel stenoses). Bardelli et al[15] investigated ACC_{max}, ACC_{sys}, and AT for diagnosing renal artery stenosis. This study showed better sensitivity, specificity, positive predictive value, and negative predictive value for ACC_{max} compared to ACC_{sys} and AT. Furthermore, the study described a potential source of bias in the measurement of ACC_{sys}, and AT is represented by the shape of the Doppler spectra. To circumvent this bias, maximal systolic acceleration (ACC_{max}) was introduced. Importantly, ACC_{max} has been shown to have diagnostic value in renal artery stenosis,[15,16,17,18] and van Tongeren et al[13] and Buschmann et al[14] showed that ACC_{max} is an accurate noninvasive tool for diagnosing PAD, also in diabetic patients who often have a higher degree of medial calcific sclerosis. In addition, determining the severity of PAD in patients with CLI can be challenging as a result of the presence of noncompressible arteries.[12] Sung et al[32] showed no consistent tendency of the influence of the compliance on the changes in peak systolic velocity, AT, or acceleration index, thus suggesting there is also no influence in ACC_{max} when the compliance changes, as in a calcified vessel. Therefore, we conclude that ACC_{max} can be clinically superior to other noninvasive measurements, particularly in patients with diabetes and/or CLI, as ACC_{max} is measured distal to the stenosis.

Additionally, ACC_{max} can be measured quickly (data acquisition time of less than 1 minute), in contrast to ABI and TP (more than 10 minutes).[14] Finally, duplex ultrasound is widely available and relatively inexpensive, the measurements can be easily obtained from the ankle or digital arteries, and the technique is suitable for patients who cannot undergo angiography.

This study has several limitations and possible caveats that warrant discussion. ACC_{max} measured in an in vitro circulatory system may not fully reflect ACC_{max} measured in vivo in a human artery; additionally, this flow model was primarily validated for aortic circulation. However, although the flow curve was biphasic in our in vitro circulatory system, both intraluminal MAP and ACC_{max} measured without a stenosis were the same as in a patient. The collateral circulation in this in vitro circulatory system went directly to the reservoir. Hence, no impact of collateral circulation was measurable in our model. This study focused on the trend of the ultrasound parameters measured at various degrees of stenosis and on the association between ACC_{max} and the intraluminal pressure gradient but did not examine possible cutoff values, which was beyond the scope of the study. Given the clinical relevance of examining a cutoff value for diagnostic criteria for PAD, this will be investigated in a subsequent study. Because it was not possible to measure ABI or TP in our in vitro flow model, we chose to use the intraluminal pressure gradient as a measure of the severity of the stenosis. Buschmann et al[14] recently introduced a computer algorithm for ACC_{max}; in our study, we used a computer-based calculated ACC_{max} at a single representative curve. The high interobserver ICC in our study may not necessarily reflect the interobserver ICC when measuring in a human artery in vivo. The high ICC in our study could have been because we used relatively large intervals in terms of the degree of stenosis (ie, no stenosis, 50%, 70%, 80%, and 90%). Thus, the ICC for ACC_{max} measured in patients should be examined in a clinical setting.

Conclusions

We report a close correlation between ACC_{max} and the MAP gradient measured using an in vitro flow model. Specifically, we found that ACC_{max} decreased as the severity of stenosis increased. Furthermore, because of the low interobserver variability and the wide availability of the required equipment, measuring ACC_{max} may provide a robust new noninvasive technique for assessing the severity of PAD. ACC_{max} should be evaluated thoroughly in a clinical study involving patients in order to test its clinical value.

Acknowledgement

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