Published in final edited form as:

J Surg Res. 2019 March ; 235: 250–257. doi:10.1016/j.jss.2018.09.088.

Radial Artery Tonometry is Associated with Major Adverse Cardiac Events in Patients with Peripheral Artery Disease

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Abstract

Introduction: Peripheral artery disease (PAD) is associated with increased arterial stiffness, as measured by an increasing radial artery augmentation index (AIX). However, it has not yet been clearly demonstrated whether AIX is associated with adverse cardiovascular outcomes in a PAD population.

Materials and Methods: Seventy-two patients with PAD were recruited between 2011–2016. Radial artery applanation tonometry was performed at a baseline visit and the central AIX, normalized to 75 beats/min, and the peripheral AIX were calculated using pulse wave analysis. Incident major adverse cardiac events (MACE) were identified by subsequent chart review.

Results: Study subjects had comorbidities commonly associated with PAD including a high prevalence of hypertension (93%), hyperlipidemia (85%), coronary artery disease (39%), and diabetes mellitus (39%). During a median follow-up period of 34 months (IQR: 29–38), 14 patients experienced a MACE. In a univariate Cox proportional hazards model, a 10-unit increase in peripheral AIX was significantly associated with a 54% increased rate of MACE (HR: 1.54, 95% CI 1.06–2.22, $p=.02$), but central AIX, normalized to 75 beats/min was not (HR: 1.33, 95%

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Author Contributions: JLR and SMG were involved in the conception and the design of the study. JLR, GJZ, KAS, SAK, and MSS were involved in the collection of the data. All of the authors were involved in the analysis and interpretation of the data. JLR and NKH were involved in the statistical analysis. JLR wrote the initial manuscript. All of the authors were involved in critically revising and editing the article. All of the authors gave a final approval of the manuscript. SMG maintained overall responsibility of the study and the manuscript.

Declaration of Conflicting Interests: The authors have no conflicts of interest to report.

Note to the Editor: An abstract of this work was presented at the Society for Vascular Medicine 29th Annual Scientific Sessions in Chicago, IL, June 13th–16th, 2018.

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CI 0.71–2.47, $p=.37$). In a multivariable model adjusted for coronary artery disease, age, and Rutherford category the peripheral AIX remained significantly associated with MACE (HR: 1.70, 95% CI 1.10–2.62, $p=.02$).

Conclusions: Increased arterial stiffness, as measured by the peripheral AIX, was independently associated with an increased rate of MACE in patients with PAD. The use of radial artery tonometry should be contemplated as a tool for risk stratification in patients with PAD.

Keywords

Peripheral artery disease; arterial stiffness; radial artery tonometry; augmentation index; adverse cardiovascular events

INTRODUCTION

Peripheral artery disease (PAD) is a disease of systemic atherosclerosis that is often characterized by impaired quality of life secondary to claudication and limb loss.^{1, 2} However, PAD is also a highly morbid and mortal disease that is strongly associated with incident and prevalent cardiovascular disease,³ a high rate of adverse cardiac events,⁴ and increased cardiovascular mortality.⁵ As the prevalence of PAD grows and continues to burden healthcare systems, the ability to risk stratify patients will become important in reducing morbidity and mortality associated with the disease. Additionally, the high prevalence of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, and diabetes mellitus typically present in patients with PAD makes existing risk stratification tools less useful in predicting cardiovascular outcomes. Several additional markers of disease have been explored and arterial structure and function have been highlighted as potential predictors of disease progression and outcomes.⁶

Arterial stiffness has been associated with atherosclerosis⁷ and is commonly evaluated directly by measuring pulse wave velocity (PWV). Measuring PWV is accomplished by analyzing the pulse wave generated by each heart beat at two points, usually the carotid and femoral arteries. This measurement has been associated with coronary artery disease (CAD) incidence⁸ and severity⁹ as well as cardiovascular-related mortality.¹⁰ Pulse wave analysis (PWA) is the assessment of the combination of a forward and reflected pulse as a single waveform.¹¹ Stiffer arteries result in an earlier return of the reflected pulse and can augment measured pressure waves. The augmented pressure is the difference in pressures between the forward and the reflected pulse, which becomes increased in stiffer arteries.^{10, 11} The augmentation index (AIX) can then be calculated by dividing the augmented pressure by the pulse pressure and then converted into a percentage.¹² Although both PWV and the AIX are commonly accepted methods of measuring arterial stiffness,¹³ the AIX can be measured using a single convenient site, commonly the radial artery. The AIX can be quickly and easily measured in a clinic setting, requires minimal training, and has standardized data that can be compared between visits, patients, or clinics. An elevated AIX has recently been reported to be independently associated with PAD,¹⁴ but there are few reports that assess the predictive role of the AIX in this patient population.

The objective of this study was to assess the relationship between arterial stiffness, as measured by the peripheral and central AIX, normalized to 75 beats/min, and incident major adverse cardiac events (MACE) in patients with PAD. We hypothesize that increased peripheral and central AIX, normalized to 75 beats/min are associated with an increased rate of MACE.

MATERIALS AND METHODS

Study Subjects

Patients with PAD presenting to the vascular surgery outpatient clinic at the San Francisco Veterans Affairs Medical Center (SFVAMC) were recruited between April 2011 and July 2016 as part of a larger cross-sectional study, with a subset of 72 patients having high quality arterial tonometry testing. Patients were defined as having PAD if they had symptoms of claudication and an ankle-brachial index (ABI) <0.9 or if they had a prior history of peripheral revascularization for symptomatic PAD, regardless of ABI. Exclusion criteria included age under 35 years old, the presence of severe hepatic (Child-Pugh B), renal (creatinine ≥ 2 mg/dL), or non-vascular inflammatory disease. Patients were also excluded if they had a severe acute illness within the last 30 days. In order to accurately consider the impact of inflammatory profiles on arterial stiffness, patients were not eligible if they were taking any immunosuppressive medications or steroids. Additionally, since this study only included patients with claudication, which was defined as Rutherford categories 1–3 or a history of revascularization for claudication, patients with critical limb ischemia were excluded. The Committee on Human Research (Institutional Review Board) at the University of California, San Francisco and the SFVAMC Research and Development Office granted this study institutional review board approval. All participants gave informed written consent.

Measurements

Demographics, Medical Comorbidities, and Anthropometrics—Study subjects attended a baseline visit and completed an intake questionnaire that collected demographic variables including age, sex, and race. A thorough medical history and electronic medical record chart review identified smoking history and the presence of medical comorbidities including hyperlipidemia, hypertension, diabetes, and CAD. Information on current use of aspirin, beta-blockers, statins, or ACE-inhibitors was provided by the patient. Height and weight were measured to calculate body mass index (BMI). Brachial artery blood pressure was measured in each patient as well as an ABI for each lower extremity using previously established techniques.¹⁵

Radial Artery Tonometry—All radial artery tonometry measurements were done at a baseline visit using the SphygmoCor® system (AtCor Medical, Sydney, Australia).¹² All measurements were performed using previously described techniques.¹⁴

The details of radial artery tonometry and how to calculate the AIX have been previously published.¹² In brief, the AIX can be calculated using PWA due to the observation that the arterial waveform being examined is a composite of an antegrade pulse wave plus a

component of the preceding wave that was reflected backward off of the arterial wall. Stiffer arteries result in higher augmented pressures due to the collision and combination of antegrade and retrograde waves.^{16, 17} Calculation of the AIX, defined as [augmented pressure/(systolic blood pressure – diastolic blood pressure)], was done using the SphygmoCor®'s proprietary software.¹² The peripheral AIX was calculated directly and the central AIX was approximated using previously validated transfer equations¹⁸ that are routinely used.^{19–21} Since the central AIX is sensitive to variations in heart rate, all measurements were normalized to 75 beats/min using the system's software.^{22, 23}

In order to ensure accurate readings, a quality index was calculated using the device's software. This quality index takes into account several parameters of variation in the recorded waveforms including pulse height variation and diastolic length variation.¹⁴ A higher quality index is characterized by less variation. A score of at least 80, set by the manufacturer, is considered to be a reading with acceptable quality. In order to ensure accuracy and quality, up to four recordings were conducted for each participant and the measurement with the highest quality index was recorded. Two co-authors (GJZ and KAS) followed a protocol developed in compliance with manufacturer guidelines to rate the quality of all tonometry data. The reviewers achieved a 100% inter-rater agreement. Data that had a quality index score of <80 or failed to meet two of the following three criteria were discarded: 1) pulse height > 80, 2) height variation > 5%, and 3) diastolic variation > 5%. Eight participants had low quality tonometry data and were excluded from this study. Based upon these standards, all 72 participants included in this study had high quality radial artery tonometry data and were included in the analyses. Two participants had a peripheral AIX greater than three standard deviations above the study mean and were therefore not included in analyses of peripheral AIX.

Laboratory Tests—At a baseline visit, a blood sample was obtained from each subject to measure plasma triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hsCRP). Plasma was assayed for these analytes the same day as collection per standard methodology (Beckman Coulter Analyzer).

Major Adverse Cardiac Events—With enrollment in the study as the time of origin and December 2016 as the end of study period, subject electronic medical records were reviewed for the subsequent occurrence of MACE, which were defined as myocardial infarction (MI), coronary revascularization, transient ischemic attack (TIA), stroke, or death from a cardiac cause.^{24, 25} MI was defined as a detected rise in cardiac markers >99th percentile with at least one of the following: 1) ischemic symptoms, 2) new ST elevation or left bundle branch block, 3) development of Q waves, 4) imaging evidence of loss of viable myocardium, or 5) coronary thrombus identified by coronary angiography.

Statistical analysis

All statistical analyses were performed using STATA version 15.0 (StataCorp, College Station, Texas). All variables were inspected for normality and linearity. Summary statistics were reported using mean and standard deviation for continuous variables along with

frequency and percentage for categorical variables. Summary statistics were also reported for patients who went on to develop a MACE and for those who did not. Baseline characteristics were compared between patients who experienced a MACE and those who did not, using a Student's *t*-test for continuous variables and a Fisher's exact test for categorical variables.

Cox proportional hazards models were used to calculate hazard ratios for MACE, using enrollment in the study as the time of origin. Univariate models were built using peripheral AIX and central AIX, normalized to 75 beats/min as the primary predictor of MACE. Then, in order to adjust for patient demographics and comorbidities that may account for an increased risk of MACE, a multivariable model was built for the peripheral AIX. The multivariable model was built by running bivariate analyses with peripheral AIX as the primary predictor and patient characteristics as covariates. Any covariate associated (at the level of $p \leq .10$) with MACE was included in the multivariable model. Several sensitivity analyses including additional covariates in the multivariable model were completed.

RESULTS

There was a total of 72 participants and the cohort was predominately male (96%) and Caucasian (69%) with an average age of 69.4 ± 6.5 years old. At baseline, subjects had a high prevalence of comorbidities that are commonly associated with PAD including CAD, diabetes mellitus, hypertension, and hyperlipidemia (Table 1). Similarly, statin, aspirin, beta-blocker, and ACE-inhibitor use was reflective of the comorbidities represented in this cohort. There were no significant differences in baseline characteristics of patients who went on to experience a MACE when compared to those who did not, however, patients who experienced a MACE were older (72.2 vs 68.7 , $p = .07$). Although not statistically significant, patients who went on to experience a MACE had a greater mean peripheral AIX at baseline than patients who remained event-free (97.7 vs 90.4 , $p = .10$) (Table 2).

During a median follow-up period of 34 months (IQR: 29–38), 14 patients experienced a MACE (event rate of 19%). These events included: eight myocardial infarctions or coronary revascularizations, four deaths from a cardiac cause, one stroke, and one TIA. Unadjusted Cox proportional hazards models identified a significant association between the peripheral AIX and rate of MACE (HR: 1.54, 95% CI: 1.06 to 2.22, $p = .02$) (Table 3). An additional sub-analysis demonstrated a higher risk of MACE when comparing higher (fourth quartile) to lower (first quartile) peripheral AIX (Figure 1). Although the central AIX, normalized to 75 beats/min was associated with an increased rate of MACE, this relationship was not statistically significant.

In bivariate analyses, age, CAD, and Rutherford category were significantly related to the peripheral AIX and rate of MACE (Table 4). In a multivariable model including age, CAD, and Rutherford category, the peripheral AIX was significantly associated with MACE with a 70% increased rate of MACE per 10-unit increase in peripheral AIX (HR: 1.70, 95% CI: 1.10 to 2.62, $p = .02$). An interaction between the peripheral AIX and CAD status and the peripheral AIX and Rutherford score were both tested for and neither were statistically significant. Sensitivity analyses including the following additional covariates in the

multivariable model did not significantly alter the relationship between the peripheral AIX and MACE: ABI (HR: 1.75, 95% CI: 1.12 to 2.71, $p=.01$), hsCRP (HR: 1.69, 95% CI: 1.10 to 2.60, $p=.02$), eGFR (HR: 1.62, 95% CI: 1.04 to 2.51, $p=.03$), and pack years smoked (HR: 1.67, 95% CI: 1.05 to 2.65, $p=.03$). Results of these sensitivity analyses suggest that the association between the peripheral AIX and incident MACE is independent of several previously reported predictors of MACE.

DISCUSSION

In a cohort of patients with PAD, increased peripheral AIX was associated with an increased rate of MACE, independent of age, CAD, and Rutherford category. We did not observe a statistically significant association between the central AIX, normalized to 75 beats/min and MACE. These findings suggest that increased stiffness of the peripheral arteries, as measured specifically by the peripheral AIX, may play a predictive role in patients with PAD independent of previously reported and validated measures of cardiac risk. Given the ease of measuring radial artery tonometry in a clinic setting, these results suggest that radial artery tonometry could be a useful tool in risk stratifying patients with PAD.

Consistent with the results of this study, increased arterial stiffness, measured by PWV or the AIX, has been reported to increase cardiovascular risk in several patient populations. Willum-Hansen *et al.* reported in a cohort of previously healthy Danish patients that increased PWV was independently associated with incidence of CAD and cardiovascular-related mortality.²⁶ In patients with pre-existing CAD, PWV was also reported to be significantly associated with incidence of MACE.²⁷ In a similar population, Weber *et al.* also reported that the AIX was significantly associated with incidence of MACE.²⁸ The results of these studies are consistent with a recent meta-analysis of prospective studies assessing the relationship between PWV and incidence of cardiovascular disease, CAD, and stroke.²⁹ Additionally, Mitchell *et al.* reported in the Framingham Heart Study that including measurements of arterial stiffness (PWV) in addition to traditional cardiac risk factors improved the prediction of a first cardiovascular event in a community-based sample.¹⁰

Although there are data linking increased arterial stiffness with MACE in patients with CAD, there is limited data assessing this relationship in cohorts that are specific to PAD. In a study of 62 patients admitted for symptomatic PAD, cardiac, or carotid disease, PWV was significantly associated with decreased ABI,³⁰ which is itself a robust predictor of poor outcomes in patients with PAD.³¹ A sensitivity analysis of the current study adjusted the Cox proportional hazards model by ABI, which did not largely alter the results. This suggests that the peripheral AIX has additional predictive value, independent of ABI, which is a traditional measure of arterial stiffness and has been associated with MACE. Brewer *et al.* reported in 106 patients with claudication that the AIX had a significant negative association with impaired walking ability,³² which has been associated with an impaired quality of life. Decreased quality of life has been associated with an increased mortality in patients with PAD.³³ A prospective study of 117 patients with symptomatic PAD in Estonia, reported that the aortic AIX was higher in patients who went on to have a cardiovascular-related death when compared to those who did not, however, this was not statistically significant in Kaplan-Meier survival analysis.³⁴ In the same study, small artery elasticity was

significantly associated with cardiovascular-related mortality in Kaplan-Meier survival analyses. However, this study only assessed the relationship between the aortic AIX (central AIX) and mortality and did not collect data on the peripheral AIX or the incidence of cardiac events. It is possible that peripheral artery stiffness, rather than central artery stiffness, plays a larger role in the development of adverse cardiac events in patients with PAD.

There are several potential mechanisms that can account for a relationship between arterial stiffness and incidence of MACE. Inflammation has been associated with the development of atherosclerosis,³⁵ arterial stiffness,³⁶ and an increased risk of adverse cardiac events.^{4, 37} Although the mechanisms underlying these relationships remain incompletely understood, hsCRP has been shown to decrease endothelial expression of nitric oxide synthase expression,³⁸ which may result in vascular stiffening.³⁹ This suggests that elevated systemic and local inflammation observed in PAD³⁵ may account for increased arterial stiffness and adverse cardiac events. However, a sensitivity analysis adjusting for hsCRP did not significantly alter the relationship between peripheral AIX and MACE in the current study. This suggests that inflammation may only account for a portion of the relationship between arterial stiffness and adverse cardiac events. It is also possible that hsCRP alone does not adequately capture a patient's total inflammation status.

The development of arterial stiffness has also been attributed to changes in the extracellular matrix (ECM). These changes include the fragmentation of elastin fibers and deposition and cross-linking of collagen.⁴⁰ These alterations in the ECM increase the migration and proliferation of smooth muscle cells,⁴¹ thrombosis,⁴² expression of vascular adhesion molecules,⁴³ endothelial permeability,⁴⁴ cholesterol deposition,⁴⁵ and atherosclerotic plaque severity.⁴⁶ Although not all of these changes have been directly associated with adverse cardiac events, these mechanisms may underlie the link between arterial stiffness, atherogenesis, and atherosclerotic plaque instability, which may mediate the increased risk of adverse cardiovascular events observed in this study.

Although arterial stiffness would seem to be a permanent characteristic, several interventions have been reported to improve arterial stiffness including smoking cessation, weight loss, increased physical activity,⁴⁷ and several anti-hypertensive medications,⁴⁸ anti-inflammatory medications,⁴⁹ and statins.⁴⁹ However, there are currently no studies to our knowledge that have examined whether utilizing the AIX as a therapeutic target, results in improvements in the incidence of cardiovascular disease, cardiac outcomes, or postoperative outcomes. Future prospective studies should further examine the role of the peripheral AIX in predicting adverse cardiovascular events and should assess whether reductions in the peripheral AIX results in improved outcomes in patients with PAD.

Limitations

The study design limits the ability to make causal or directional conclusions and only associations can be reported. The small sample size and the small number of events reduces power and impairs the ability to include more covariates in the multivariable Cox proportional hazards models. Several sensitivity analyses were performed in order to

demonstrate that the relationship between the peripheral AIX and MACE was independent of several individual patient characteristics including ABI, however, including all of these covariates in one large multivariable model might have produced different results. This was not possible due to concerns for overfitting the model. All patients included in this study were Veterans and were representative of the VA population (mostly male and Caucasian), thus the results may not be generalizable to the general population.

CONCLUSION

In summary, we report that increased arterial stiffness, as measured by the peripheral AIX, is associated with an increased rate of MACE in patients with PAD. These findings suggest that increased stiffness of the peripheral arteries may play a predictive role in patients with PAD. These findings inform future studies and suggest that the peripheral AIX may be utilized to riskstratify patients with PAD.

Funding Acknowledgement:

This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through University of California, San Francisco-Clinical and Translational Science Institute Grant Number TL1 TR001871 with additional student research support from the Society for Vascular Surgery Student Research Fellowship Award and the American Heart Association Student Scholarship (JLR). Furthermore, this work was supported by start-up funds from the University of California, San Francisco and the Northern California Institute for Research and Education, by Award Number KL2RR024130 from the National Center for Research Resources, Award Number 1K23HL122446-01 from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI), and a Society for Vascular Surgery Seed Grant and Career Development Award (SMG). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. The funding organizations were not involved in the design and conduct of the study, collection, management, analysis, and interpretation of the data, or preparation, review or approval of the manuscript.

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AIX = augmentation index; MACE = major adverse cardiac events.

Figure 1.

Kaplan-Meier sub-analysis demonstrating that increased peripheral augmentation index is associated with an increased rate of major adverse cardiac events in patients with peripheral artery disease (Log-rank: $p=.06$). The curves have been truncated where the standard error exceeds 10%.

Table 1.

Baseline Characteristics of Study Subjects

	Whole Study Group (n=72)	MACE (n=14)	No MACE (n=58)	<i>P</i> value ^a
Characteristics				
Age (years)	69.4 ± 6.5	72.2 ± 7.6	68.7 ± 6.1	.07
Male sex	69 (96%)	13 (93%)	56 (97%)	.48
Caucasian	50 (69%)	12 (86%)	38 (66%)	.20
Body mass index (kg/m ²)	28.5 ± 5.3	27.5 ± 4.8	28.7 ± 5.5	.45
Pack years	43.9 ± 30.8	44.3 ± 41.1	43.8 ± 28.3	.96
Index ABI	0.75 ± 0.15	0.74 ± 0.21	0.75 ± 0.14	.92
Rutherford Category				
No claudication	4 (6%)	2 (14%)	2 (3%)	.43
Mild claudication	26 (36%)	4 (29%)	22 (38%)	
Moderate claudication	18 (25%)	3 (21%)	15 (26%)	
Severe claudication	24 (33%)	5 (36%)	19 (33%)	
Comorbidities				
Hypertension	67 (93%)	13 (93%)	54 (93%)	.99
Hyperlipidemia	61 (85%)	10 (71%)	51 (88%)	.21
Type 2 diabetes mellitus	28 (39%)	3 (21%)	25 (43%)	.22
Coronary artery disease	28 (39%)	8 (57%)	20 (34%)	.14
Systolic blood pressure (mmHg)	143 ± 20	141 ± 22	143 ± 20	.77
Diastolic blood pressure (mmHg)	78 ± 11	74 ± 11	79 ± 11	.20
Medications				
Aspirin	55 (76%)	9 (64%)	46 (79%)	.30
ACE-inhibitor	38 (53%)	5 (36%)	33 (57%)	.23
Beta-blocker	43 (60%)	7 (50%)	36 (62%)	.55
Statin	56 (78%)	10 (71%)	46 (79%)	.50
Laboratory Studies				
Total cholesterol (mg/dL)	162 ± 40	167 ± 48	161 ± 38	.65
LDL (mg/dL)	87 ± 35	90 ± 45	86 ± 33	.68
HDL (mg/dL)	48 ± 14	49 ± 8	48 ± 15	.76
Triglycerides (mg/dL)	141 ± 94	136 ± 68	142 ± 100	.85
eGFR (mL/min)	75 ± 21	76 ± 29	74 ± 20	.77
Albumin (g/dL)	4.1 ± 0.3	3.9 ± 0.4	4.1 ± 0.3	.15
HbA1c (%)	6.3 ± 1.4	6.1 ± 1.7	6.3 ± 1.3	.58
hsCRP (mg/L)	3.7 ± 3.4	2.8 ± 2.5	3.9 ± 3.6	.32

Values as "mean ± one standard deviation" or "n (%)". ABI = ankle-brachial index; ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtrate rate; HDL = high-density lipoprotein; HbA1c = hemoglobin A1c; hsCRP = high-sensitivity C-reactive protein; LDL = low density lipoprotein; MACE = major adverse cardiac event.

^aComparing MACE vs No MACE. Calculated using a Fisher's exact test for categorical variables or a Student's *t*-test for continuous variables.

Table 2.

Baseline Radial Artery Tonometry of Study Subject

Characteristics	Whole Study Group (n=72)	MACE (n=14)	No MACE (n=58)	<i>P</i> value ^b
Central Artery Stiffness				
Central Systolic Pressure (mmHg)	134 ± 19	134 ± 19	135 ± 20	.94
Central Diastolic Pressure (mmHg)	79 ± 14	77 ± 13	79 ± 15	.57
Central Augmentation Index	31.9 ± 9.4	33.9 ± 11.3	31.5 ± 8.9	.40
Central Augmentation Index at 75bpm	26.0 ± 9.3	27.0 ± 12.4	25.7 ± 8.5	.64
Peripheral Artery Stiffness^a				
Peripheral Systolic Pressure (mmHg)	144 ± 19	144 ± 18	144 ± 20	.96
Peripheral Diastolic Pressure (mmHg)	79 ± 12	76 ± 13	79 ± 11	.36
Peripheral Mean Pressure (mmHg)	101 ± 13	98 ± 13	102 ± 13	.31
Peripheral Augmentation Index	91.8 ± 14.8	97.7 ± 19.8	90.4 ± 13.0	.10

Values as “mean ± one standard deviation”. MACE = major adverse cardiac event.

^aPeripheral tonometry data summarizes all values after two outliers >3SD from the mean were dropped.

^bComparing MACE vs No MACE. Calculated using a Student’s *t*-test.

Table 3.

Univariate Cox Proportional Hazards for Predicting MACE (n=72)

Predictor*	Univariate Analysis		
	HR	95% CI	P value
Peripheral AIX	1.54	1.06 to 2.22	.02
Central AIX at 75 bpm	1.33	0.71 to 2.47	.37

Boldface *p* values were below the .05 level required for statistical significance. AIX = augmentation index; bpm = beats per minute; MACE = major adverse cardiac event.

*
Per 10-unit change

Table 4.

Cox Proportional Hazards for Peripheral AIX Predicting MACE (n=72)

Predictor	Bivariate Analysis			Multivariable Analysis ^a		
	HR	95% CI	P value	HR	95% CI	P value
Peripheral AIX* (per 10-unit change)	-	-	-	1.70	1.10 to 2.62	.02
Age (years)	1.06	0.99 to 1.14	.08	1.06	0.99 to 1.14	.10
Caucasian	2.95	0.66 to 13.29	.16	-	-	-
Body mass index (kg/m ²)	0.97	0.87 to 1.09	.64	-	-	-
Pack years	1.00	0.98 to 1.02	.81	-	-	-
Type 2 diabetes mellitus	0.54	0.14 to 2.07	.37	-	-	-
Coronary artery disease	2.56	0.87 to 7.54	.09	4.70	1.30 to 17.00	.02
Hypertension	0.87	0.11 to 6.89	.89	-	-	-
Hyperlipidemia	0.37	0.11 to 1.21	.11	-	-	-
Index ABI	0.63	0.01 to 31.4	.82	-	-	-
Rutherford category: ref No claudication	-	-	-	-	-	-
Mild claudication	0.14	0.02 to 0.85	.03	0.11	0.02 to 0.78	.03
Moderate claudication	0.11	0.02 to 0.75	.02	0.07	0.01 to 0.58	.01
Severe claudication	0.14	0.02 to 0.81	.03	0.06	0.01 to 0.45	.01
Aspirin	0.69	0.23 to 2.07	.51	-	-	-
Statin	0.62	0.19 to 2.08	.44	-	-	-
Beta-blocker	0.64	0.22 to 1.87	.42	-	-	-
ACE-inhibitor	0.66	0.21 to 2.05	.47	-	-	-
eGFR (mL/min)	1.00	0.98 to 1.03	.80	-	-	-
hsCRP (mg/L)	0.89	0.72 to 1.10	.28	-	-	-

Boldface *p* values were below the .05 level required for statistical significance in the multivariable model. ABI = anklebrachial index; ACE = angiotensin-converting-enzyme; AIX = augmentation index; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MACE = major adverse cardiac event.

^a All variables with a *p*-value .10 in bivariate analysis were included in the multivariable model.

* The primary predictor was run as a univariate analysis prior to inclusion in the multivariable model.