Relation of Brachial and Digital Measures of Vascular Function in the Community
The Framingham Heart Study

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Abstract—Impaired vascular function contributes to the development of clinical cardiovascular disease. The relation between vasodilator function assessed noninvasively in the brachial and digital arteries remains incompletely defined. In the Framingham Offspring, Third Generation and Omni Cohorts, we measured flow-mediated dilation (FMD; n=7031; age 48±13 years; age range, 19 to 88 years; 54% women) and peripheral arterial tonometry (PAT) ratio (n=4352; 55±16 years; age range, 19 to 90 years; 51% women). Abnormal vascular function for each measure was defined by the sex-specific fifth percentile in a reference group free of conventional cardiovascular risk factors. The prevalence of abnormal FMD but not abnormal PAT ratio was higher with advancing age. In multivariable models, higher body mass index was associated with a higher prevalence of both abnormal FMD and PAT ratio. Additional correlates of abnormal FMD included increasing age and higher systolic blood pressure. In contrast, correlates of abnormal PAT ratio included lower systolic blood pressure, increasing total/high-density lipoprotein cholesterol ratio, diabetes, smoking, and lipid-lowering medication. Whereas women had higher FMD and PAT ratios compared with men, using sex-specific reference values, women had a higher prevalence of abnormal brachial and digital vascular function. In participants who had concurrent testing (n=1843), PAT ratio was not significantly associated with FMD in multivariable models. In this large, community-based cohort, brachial and digital measures of vascular function had differing relations with cardiovascular risk factors and were nearly uncorrelated with each other. These results suggest that FMD and PAT provide distinct information regarding vascular function in conduit versus smaller digital vessels. (*Hypertension*. 2011;57:390-396.) ● Online Data Supplement

Key Words: cohort study ■ endothelium ■ epidemiology ■ risk factors ■ vascular function

Endothelial dysfunction contributes to cardiovascular risk. Impaired endothelial function, characterized by decreased nitric oxide availability, is a central mediator of atherogenesis and participates in the clinical expression of vascular disease.[1–3] The vasodilator response to increased flow has been established as a measure of vascular function in both the conduit brachial artery and the digital microcirculation.[4,5]

It is well-established that brachial flow-mediated dilation (FMD) and peripheral arterial tonometry (PAT) hyperemic response are lower in the presence of selected cardiovascular risk factors.[6–9] However, prior studies comparing brachial FMD and the PAT hyperemic response have been limited to small, selected samples.[10,11] Therefore, the present study sought to compare these 2 techniques in a large community-based sample by defining the prevalence of and risk factors related to reduced vasodilator function defined by establishing cut points for abnormal brachial and digital vascular function in a reference sample without standard cardiovascular risk factors.

Methods

Participants

The study sample was drawn from the Framingham Offspring and Third Generation Cohorts and the Omni Cohort 1, which have been described elsewhere.[12–14] The Boston University Medical Center Institutional Review Board approved the research and all participants provided written informed consent. Brachial vascular function was assessed in participants in the Offspring Cohort at the seventh examination cycle (1998 to 2001), in the Third Generation at the first examination cycle (2002 to 2005), and Omni Cohort 1 at the second examination cycle (1999 to 2001). Digital vascular function was assessed in participants in the Offspring Cohort at the eighth examination cycle (2005 to 2008) and in the Third Generation at the first examination cycle. Additional details regarding the available

vascular testing for each cohort is provided in the online supplement (available at http://hyper.ahajournals.org). We have reported previously regarding brachial vascular function in the Offspring participants and digital vascular function in the Third Generation participants.[6,7]

To generate reference samples, we excluded participants who had any of the following characteristics at the Heart Study examination: diabetes (defined as a fasting blood glucose $\geq$126 mg/dL or treatment with insulin or an oral hypoglycemic agent), current smoking (defined as smoking regularly within 12 months of the index examination), hypertension (defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg), elevated low-density lipoprotein cholesterol (defined as low-density lipoprotein cholesterol >160 mg/dL), obesity (defined as body mass index [BMI] $\geq$30 kg/m^2), hormone replacement therapy, drug treatment for hypertension, lipid-lowering medication, or prevalent cardiovascular disease. Prior clinical cardiovascular disease was determined using previously published criteria.[15] At the seventh examination cycle in the Offspring Cohort, eligible participants completed a 6-minute walk test either before or after the vascular function testing. Because completing the walk test before the vascular examination was associated with higher FMD, we excluded these participants from the reference sample.[7]

Brachial Measures of Vascular Function

Participants were asked to not eat or drink (except for water or decaffeinated coffee or tea) after 8 PM the night before the vascular test. We have reported the methodology and reproducibility for measuring brachial artery diameters and flow.[7,16] In brief, brachial artery diameter was imaged by high-resolution ultrasound (Toshiba SSH-140A, 7.5-MHz linear array transducer in Offspring and Omni and Philips Sonos 5500, 11- to 3-L linear array transducer in Third Generation) at rest and 1 minute after reactive hyperemia was induced by 5-minute cuff occlusion on the forearm. Sonographers blinded to participants' status measured arterial diameter offline using commercially available software (Brachial Analyzer; Medical Imaging Applications, Iowa City, IA; Version 3.2.3.sp2). FMD was calculated as the percent change in brachial diameter from the resting state (100*[hyperemic diameter at 60 seconds–resting diameter]/ resting diameter). Brachial artery flow was assessed using pulsed Doppler flow at rest and for 15 seconds after cuff release. Doppler recordings were analyzed in a blinded fashion using a semiautomated signal-averaging method with correction for insonation angle.[16] Resulting flow waveforms were integrated to assess mean resting and mean hyperemic flow velocities.

Digital Measures of Vascular Function

The methodology for measuring digital vascular function using PAT has been described.[6] Briefly, we assessed pulse amplitude in the fingertip at rest using a PAT device that is placed on the index finger of each hand (Endo-PAT2000; Itamar Medical, Caesarea, Israel). We induced hyperemia by a 5-minute forearm cuff occlusion on 1 arm. We recorded pulse amplitude electronically throughout the study and data were analyzed in a blinded fashion by a computerized, semiautomated algorithm (Itamar Medical). We expressed the PAT hyperemic response as previously described.[6] To determine the PAT ratio, we first calculated the ratio of the postdeflation pulse amplitude to the baseline pulse amplitude in the 90- to 120-second postdeflation time period (ie, $X_{h90-120}/X_{h0}$: with h denoting hyperemic finger and 0 denoting baseline, X being the pulse amplitude). Then, we divided this result by the corresponding ratio from the contralateral, control hand (ie, $X_{c90-120}/X_{c0}$: with c denoting the control finger and 0 denoting baseline) to obtain the PAT ratio. Because PAT ratio had a heteroscedastic error structure, we used a natural logarithm transformation in all analyses such that PAT ratio=ln[$(X_{h90-120}/X_{h0})/(X_{c90-120}/X_{c0})$].

Statistical Analyses

We defined cut points for low FMD, hyperemic flow velocity, and PAT ratio as the sex-specific fifth percentile in the appropriate reference sample. In the full sample, we determined the overall proportion of participants who had vasodilator function values less than those cut points.

To identify factors associated with low vasodilator function, we performed stepwise logistic regression models using the SAS logistic procedure.[17] Age, sex, and cohort were forced into all models. We then performed stepwise selection ($P\leq0.10$ to enter and stay in the model) from the following candidate variables: systolic blood pressure, diastolic blood pressure, heart rate, BMI, total cholesterol to high-density lipoprotein (HDL) cholesterol ratio, triglycerides, diabetes, current smoking, walk test before vascular test, hormone replacement therapy, hypertension medication, lipid-lowering medication, and prevalent cardiovascular disease. To account for within-family correlations, we refit the chosen model using generalized estimating equations with exchangeable covariance structure and logit link. In a secondary analysis, we analyzed continuous measures of vascular function in the full sample using stepwise linear regression models with the same variables listed previously. In a subgroup of Third Generation participants who had concurrent brachial and digital measurement of vascular function, we estimated partial correlations between FMD and PAT ratio accounting for (1) age and sex; and (2) age, sex, systolic blood pressure, diastolic blood pressure, heart rate, BMI, total to HDL cholesterol ratio, diabetes, current smoking, use of lipid-lowering medications, and prevalent cardiovascular disease.

All analyses were performed using SAS 9.1.[17] Two-sided $P<0.05$ was considered statistically significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Participant Characteristics

The clinical characteristics of the reference and full samples for brachial and digital vascular function are shown in Table 1. The younger mean age in the brachial versus the digital full sample reflects the measurement of brachial vascular function at an earlier examination cycle in the Offspring Cohort and the larger proportion of Third Generation participants in the brachial sample. The clinical characteristics of the subset of Third Generation participants with concurrent brachial and digital vascular testing are shown in Supplemental Table I.

Brachial and Digital Measures of Vascular Function in the Reference and Full Samples

The sex-specific mean and fifth percentile cut points that defined low FMD, hyperemic flow velocity, and PAT ratio in the reference sample are presented in Table 2. For all the vascular measures, men had lower mean vasodilator responses than women in both the reference and the full samples.

Prevalence of Low Vascular Function in the Full Samples

In the full samples, prevalence of low vasodilator function was 1.7 to 2.6 times the defined 5% prevalence in the reference samples (Table 2). As shown in the Figure, the prevalence of abnormal brachial measures of vasodilator function increased markedly with age in men and women for both FMD and hyperemic flow velocity. For example, the prevalence of low FMD was <5% in both sexes aged <30 years but reached 20% in men and 38% in women aged $\geq$70 years. In contrast, the prevalence of abnormal digital vascular function measured as PAT ratio increased only slightly across age groups: 6% in men and 9% in women aged <30 and 9% in men and 11% in women aged $\geq$70 years.

Table 1.   Participant Characteristics

| | Brachial Vascular Function | | | | Digital Vascular Function | | | |
| | Reference Sample | | Full Sample | | Reference Sample | | Full Sample | |
Characteristic	Men (N=973)	Women (N=1382)	Men (N=3273)	Women (N=3758)	Men (N=597)	Women (N=783)	Men (N=2124)	Women (N=2228)
Age, years	42±11	41±11	49±14	49±14	45±14	46±14	54±16	55±16
Systolic blood pressure, mm Hg	116±9	109±11	124±15	119±18	117±9	111±11	125±15	121±18
Diastolic blood pressure, mm Hg	74±7	70±8	77±10	73±9	75±7	70±8	76±10	73±9
Heart rate, beats/min	58±9	62±10	62±11	65±10	58±10	62±9	61±10	64±10
BMI, kg/m^2	25.6±2.6	23.4±2.9	28.3±4.7	26.7±5.9	25.6±2.6	23.6±3.0	28.4±4.7	27.0±6.0
Total cholesterol/HDL, ratio	4.0±1.1	3.0±0.8	4.4±1.3	3.4±1.1	3.9±1.1	3.0±0.7	4.0±1.2	3.3±1.0
Triglycerides, mg/dL	106±61	83±41	128±70	109±61	104±58	82±38	120±64	106±56
Fasting glucose, mg/dL	95±8	89±7	103±25	95±21	96±8	91±7	105±23	98±18
Diabetes	*	*	297 (9)	216 (6)	*	*	280 (13)	183 (8)
Smoking	*	*	508 (16)	558 (15)	*	*	296 (14)	289 (13)
Hypertension	*	*	1095 (33)	935 (25)	*	*	924 (44)	788 (35)
Elevated LDL	*	*	340 (10)	297 (8)	*	*	125 (6)	126 (6)
Obesity	*	*	932 (28)	873 (23)	*	*	625 (29)	552 (25)
Walk test before	*	*	480 (15)	599 (16)	*	*	0 (0)	0 (0)
Hormone replacement therapy	*	*	0 (0)	636 (17)	*	*	0 (0)	177 (8)
Hypertension medication	*	*	707 (22)	643 (17)	*	*	709 (33)	632 (28)
Lipid-lowering medication	*	*	550 (17)	352 (9)	*	*	667 (31)	532 (24)
Prevalent cardiovascular disease	*	*	276 (8)	149 (4)	*	*	239 (11)	142 (6)

Continuous variables, mean±SD; dichotomous variables, no. (%).
*Reference sample exclusion criterion.
LDL indicates low-density lipoprotein.

Multivariable Correlates of Low Vascular Function

Overall, the clinical correlates of abnormal brachial measures of vascular function largely differed from the clinical correlates of abnormal digital vascular function (Table 3). Based on sex-specific cut points, women had a higher prevalence than men of abnormal FMD, hyperemic flow velocity, and PAT ratio. In stepwise multivariable logistic regression models, increasing BMI was associated with abnormal FMD and PAT ratio. Factors associated with abnormal FMD and hyperemic flow responses were increasing age and systolic blood pressure. Lower diastolic blood pressure and prevalent cardiovascular disease were associated with abnormal hyperemic flow. In contrast, increasing total/HDL cholesterol ratio,

diabetes, current smoking, and lipid-lowering medication were associated with abnormal PAT ratio, but increasing systolic blood pressure was associated with a lower prevalence of abnormal PAT ratio and there was no association between age and abnormal PAT ratio. Findings were similar in generalized estimating equation models (data not shown). We performed an additional sensitivity analysis using a cut point for abnormal vascular function at the tenth percentile and found qualitatively similar risk factor relations (data not shown).

Correlation of Brachial and Digital Measures of Vascular Function

To further evaluate the relations between the brachial and digital vascular measures, we examined partial correlations in

Table 2.   Brachial and Digital Vascular Measures in the Reference and Full Samples

| | Reference Sample | | | | Full Sample | | | |
| | Mean (SD) | | Fifth Percentile | | Mean (SD) | | Abnormal Percent§ | |
	Men	Women	Men	Women	Men	Women	Men	Women
FMD, %*	4.50 (2.95)	6.84 (3.90)	0.24	0.90	3.57 (2.94)	5.37 (3.97)	10.4	12.5
Hyperemic flow velocity, cm/s†	56.8 (17.3)	64.2 (17.4)	29.2	36.7	53.6 (19.3)	60.9 (20.6)	10.9	13.0
PAT ratio‡	0.63 (0.36)	0.88 (0.36)	0.06	0.27	0.57 (0.37)	0.82 (0.40)	8.5	9.5

*Reference sample n=973 and n=1382; full sample n=3273 and n=3758 for men and women, respectively.
†Reference sample n=911 and n=1315; full sample n=2925 and n=3400 for men and women, respectively.
‡Reference sample n=597 and n=783; full sample n=2124 and n=2228 for men and women, respectively.
§Abnormal refers to percent lower than the fifth percentile of the reference group.
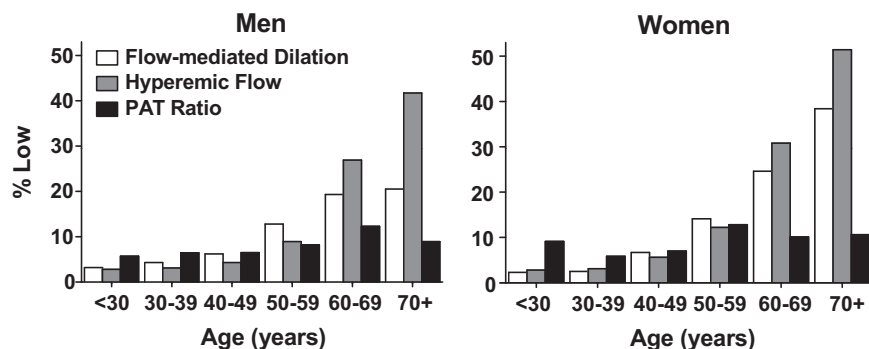
Figure. Age and abnormal vascular function. Prevalence of low FMD, hyperemic flow velocity, and PAT ratio for men and women by age group in the full samples based on the sex-specific fifth percentile threshold in the reference samples.

Third Generation participants who had both testing procedures performed concurrently. In unadjusted analyses, higher PAT ratio was associated modestly with higher FMD but not hyperemic flow velocity. However, in age- and sex-adjusted and multivariable-adjusted analyses, PAT ratio was not correlated significantly with FMD (Table 4). In a secondary analysis, we compared the PAT ratio from 60 to 90 seconds with FMD in an age- and sex-adjusted analysis and found similar results to the PAT ratio from 90 to 120 seconds (data not shown). In age- and sex-adjusted analyses there was a weak association of higher hyperemic flow velocity with lower PAT ratio that was rendered insignificant in the multivariable model (Table 4). In an additional age- and sex-adjusted analysis, we found no association of PAT ratio with FMD adjusted for hyperemic flow velocity (partial $r = -0.001$, $P = 0.98$).

Secondary Analyses

We performed stepwise linear regression models with continuous values of the brachial and digital vascular measures (Supplemental Table II). Women had higher vasodilation function than men for FMD, hyperemic flow velocity, and PAT ratio. The other clinical relations were substantially similar to the logistic models.

Discussion

In a large community-based cohort, we identified the prevalence of abnormal peripheral vasodilator function based on sex-specific cut points derived in reference samples. Overall, we found a 1.7- to 2.6-fold higher prevalence of low brachial and digital measures of vascular function in the full samples compared with the reference samples. The prevalence of low brachial measures of vascular function rose markedly with advancing age in both men and women. In contrast, digital vascular function showed a stable prevalence across decades of adult life. By examining factors associated with low vasodilator function, we identified distinct profiles in the clinical correlates of abnormal brachial and digital vascular function. In a subset of participants with simultaneous measurements, we observed no statistically significant relation between PAT hyperemic response and FMD or hyperemic flow. Thus, our findings suggest that digital and brachial measures of vasodilation reflect distinct aspects of vascular function.

In prior studies, digital vascular function has been related to vasodilator function in conduit vessels. PAT hyperemic response correlated with FMD in patients referred for chest pain evaluation and a small group of healthy individuals.[10,11] Our apparently discrepant findings may be attributable to a

Table 3.   Relations Between Vascular Risk Factors and Abnormal Brachial or Digital Vasodilator Function

	Abnormal PAT Ratio		Abnormal FMD Percent		Abnormal Hyperemic Flow Velocity	
	OR* (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.08 (0.87–1.33)	0.48	1.44 (1.28–1.63)	<0.0001	1.91 (1.64–2.22)	<0.0001
Female sex	1.41 (1.12–1.78)	<0.01	1.30 (1.10–1.54)	<0.01	1.36 (1.14–1.62)	<0.001
Systolic blood pressure	0.71 (0.63–0.81)	<0.0001	1.44 (1.33–1.56)	<0.0001	2.07 (1.85–2.30)	<0.0001
Diastolic blood pressure	. . .	. . .	. . .	. . .	0.86 (0.77–0.96)	<0.01
Heart rate	1.15 (1.04–1.28)	<0.01	. . .	. . .	. . .	. . .
BMI	1.30 (1.17–1.44)	<0.0001	1.18 (1.09–1.27)	<0.0001	. . .	. . .
Total/HDL cholesterol ratio	1.36 (1.22–1.51)	<0.0001	. . .	. . .	. . .	. . .
Diabetes	1.73 (1.28–2.34)	<0.001	. . .	. . .	. . .	. . .
Current smoker	1.97 (1.48–2.60)	<0.0001	. . .	. . .	. . .	. . .
Lipid-lowering medication	1.43 (1.10–1.86)	<0.01	. . .	. . .	. . .	. . .
Cardiovascular disease	. . .	. . .	. . .	. . .	1.52 (1.15–2.00)	<0.01

*ORs are expressed for presence of categorical variables and per 1 SD for continuous variables. Dashes indicate that the variable did not enter the stepwise model. In additional to the covariates listed, potential covariates included: triglycerides, walk test before vascular test, hormone replacement therapy, and hypertension medication. All models adjust for age, sex, and cohort.

Table 4. Relations Between Digital and Brachial Vascular Function (N=1843)

Adjustment	FMD Percent		Hyperemic Flow Velocity	
	r*	P	r*	P
PAT ratio				
Unadjusted	0.094	<0.001	0.007	0.77
Age and sex	−0.012	0.61	−0.052	0.03
Multivariable†	−0.009	0.70	−0.026	0.27

*For age and sex and multivariable-adjusted models, partial r for PAT ratio is provided.

†Multivariable model includes: age, sex, systolic blood pressure, diastolic blood pressure, heart rate, BMI, total/HDL cholesterol ratio, diabetes, current smoking, hormone replacement therapy, hypertension therapy, lipid-lowering medication use, and prevalent cardiovascular disease.

number of distinguishing factors. Prior studies did not adjust for relevant clinical covariates and found a relation consistent with our findings in unadjusted models. Our larger sample permits adjustment for clinical covariates and found lack of association when adjusting for age and sex. In addition, our cohort is unselected, has a low overall prevalence of clinical cardiovascular disease, and may represent an earlier stage of vascular dysfunction. It is conceivable that an association of brachial and digital vascular function will be observed in patients who are older or who have more advanced vascular disease.

The present study extends prior work by comparing the risk factor relations with abnormal vasodilator function in the brachial and digital vessels. The clinical factors associated with low brachial FMD included advancing age, female sex, higher systolic blood pressure, and BMI. Risk factors associated with abnormal brachial reactive hyperemia included advancing age, female sex, higher systolic blood pressure, lower diastolic blood pressure, and prevalent cardiovascular disease. The set of risk factors associated with increased odds of low digital vascular function were largely different and included metabolic risk factors, including higher BMI, higher cholesterol, and the presence of diabetes as well as smoking and female sex. Lower systolic blood pressure was also associated with abnormal PAT ratio. The concordant escalating prevalence of abnormal microvessel and conduit vessel function with increasing BMI suggests broad-based alterations in vasodilator function in the setting of obesity. Overall, a different pattern emerged for the risk factor relations with abnormal brachial and digital vascular function that may reflect the distinct circulations and vascular responses assessed with each technique.

Investigators have proposed each vasodilator measure (FMD, reactive hyperemic, and PAT hyperemic response) as noninvasive assessments of endothelial function.[4,18] There is evidence demonstrating the role of nitric oxide bioavailability in each vascular response.[19,20] However, an array of additional substances, including prostaglandin, adenosine, hydrogen peroxide, and others, have been shown to determine vasodilation in response to shear stress and ischemia.[21] The heterogeneity that we observed across the vasodilator measures may be attributable to variable contribution of diverse vasodilator mechanisms to each response. It is possible that dependence on endothelium-independent vasodilator substances explains the relation of the PAT ratio and the brachial hyperemic flow response in age- and sex-adjusted models. In addition, physiological differences based on vessel size may underlie the divergent brachial and digital reactivity. The PAT hyperemic response represents digital microvessel vasodilation, whereas brachial hyperemia assesses mostly forearm microvascular response, and FMD assesses conduit artery vasodilation. The dual circulation in the finger composed of both capillaries and arteriovenous anastomoses may have a differential physiological response to ischemia.[22] In distinction with FMD, the PAT hyperemic response is adjusted for any changes that occur in the control arm. Our findings are consistent with the possibility that vascular bed and vessel size determine sensitivity to early damage by specific cardiovascular risk factors.

We observed divergent patterns in the prevalence of abnormal brachial and digital vascular function across the decades of adult life. The prevalence of reduced FMD and reactive hyperemia increased substantially with advancing age in men and women, rising particularly steeply after age 50 years. Our findings are consistent with prior reports of an association between increasing age and lower FMD that has been attributed to alterations in the production of nitric oxide and oxidant species.[7,23,24] In striking contrast, the prevalence of low PAT hyperemic response showed little variability with advancing age. Our unexpected findings may potentially be explained by a different response of the finger vessels to aging. We can speculate that there are counterbalancing physiological changes in the hand microvessels with aging that tend to preserve distal vessel hyperemic responses as measured with the PAT device. It is also possible that the PAT hyperemic response lacks sensitivity to detect the effects of aging due to the presence of arteriovenous anastomoses in the human finger.[22]

We delineated reference limits for a broad set of noninvasive vascular function measures. To derive sex-specific reference values, we determined the distribution of each measure in a large group of healthy individuals without established clinical cardiovascular disease or risk factors. Thresholds defining low vasodilation function based on the fifth percentile were higher in women than men for FMD, reactive hyperemic, and PAT hyperemic response. Based on sex-specific definitions of abnormal vascular function, women were more likely to be classified as abnormal compared with men for all 3 vascular function measures. In linear models, women had higher values for brachial and digital vascular function consistent with prior reports.[6,7,25] The higher prevalence of abnormal vascular function in women using sex-specific reference groups may reflect the lower risk factor burden in women in the reference sample compared with men. It is also possible that differences in the distribution of menstrual status between the reference and full samples may have contributed. Our results suggest that in the presence of comparable risk factor exposure, women are more likely to experience abnormal vascular function and are consistent with prior reports indicating that women have

higher cardiovascular risk associated with certain cardiovascular risk factors.[26]

Several risk factor relations with abnormal brachial and digital vascular function were unexpected. The relation between lipid-lowering therapy and increased prevalence of abnormal digital vasodilation likely reflects indication bias in our observational study. Surprisingly, increasing systolic blood pressure was associated with lower prevalence of abnormal PAT ratio. We speculate that elevated blood pressure may lead to increased microvascular compliance due to changes in tone or structure that in turn produce higher hyperemic pulse amplitude in the digit. Furthermore, the presence of adverse microvascular remodeling produced by elevated blood pressure may not be detectable using the PAT device because the pulse amplitude measured by PAT depends on pulse pressure that in older individuals is largely determined by systolic blood pressure.[27] Alternatively, the use of antihypertensive medications could have different influences on the digital circulation.

The observed thresholds for FMD and reactive hyperemia are considerably lower than values associated with increased event rates in longitudinal studies.[2,28,29] It is important to note that the reference limits described in the current study are defined empirically and not based on disease status or cardiovascular disease risk assessed prospectively. In addition, the measurement approach for brachial vascular function differs across studies, including forearm cuff placement, in the current study. Vasodilator responses below our reference limits, therefore, do not necessarily signify presence of vascular disease or a heightened cardiovascular disease risk.

Several limitations of the current study must be considered. The majority of the participants were white; thus, the reference limits may not be generalizable to other racial and ethnic groups. We lacked power to examine specific minorities in our multiracial Omni Cohort. In the Offspring Cohort, measurement of brachial and digital vascular function was not performed at the same examination and was separated by up to 10 years. It is possible that temporal factors or the use of different ultrasound machines in the Offspring compared with the Third Generation may account for some of the observed differences in the risk factor relations of the 2 techniques. The study design did not include repeated measures of vascular function. However, our approach of identifying contemporaneous reference groups and determining thresholds for abnormal values in the same fashion for each measure facilitated comparison of the risk factor relations with abnormal brachial and digital vascular function. The community-based design precluded administration of nitroglycerin; thus, we cannot comment on the proportion of endothelium-independent vasodilation for either the brachial or digital vascular responses. The cross-sectional and observational design of our study prevents any causal inferences and precise determination of mechanisms producing abnormal vasodilator responses. Strengths of our study include a large sample size, a community-based cohort, and assessment of a comprehensive set of vascular function measures as well as cardiovascular risk factors.

Perspectives
Differential patterns of risk factor relations emerge for abnormal brachial and digital vascular function in the community. The divergence between brachial and digital vascular function emphasizes the possibility that vasodilation may vary significantly with vessel size and location. The complexity of arterial physiology across vascular beds may have implications for the use of the PAT test to measure vascular function. Taken together, our findings suggest that the measurement of the PAT hyperemic response provides a distinct, nonequivalent assessment of vascular function as compared with measurement of brachial artery vasodilator function. Further studies are needed to evaluate the relative contribution of each vascular measure to cardiovascular risk prediction.

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