Stroke

CLINICAL AND POPULATION SCIENCES

Digital Peripheral Arterial Tonometry and Cardiovascular Disease Events

The Framingham Heart Study

Leroy L. Cooper, PhD, MPH; Na Wang, MA; Alexa S. Beiser, PhD; José Rafael Romero, MD; Hugo J. Aparicio, MD, MPH; Vasileios-Arsenios Lioutas, MD; Emelia J. Benjamin, MD, ScM; Martin G. Larson, ScD; Ramachandran S. Vasan, MD; Gary F. Mitchell, MD; Sudha Seshadri, MD; Naomi M. Hamburg, MD, MS

BACKGROUND AND PURPOSE: Novel noninvasive measures of vascular function are emerging as subclinical markers for cardiovascular disease (CVD) and may be useful to predict CVD events. The purpose of our prospective study was to assess associations between digital peripheral arterial tonometry (PAT) measures and first-onset major CVD events in a sample of FHS (Framingham Heart Study) participants.

METHODS: Using a fingertip PAT device, we assessed pulse amplitude in Framingham Offspring and Third Generation participants (n=3865; mean age, 55±14 years; 52% women) at baseline and in 30-second intervals for 4 minutes during reactive hyperemia. The PAT ratio (relative hyperemia index) was calculated as the post-to-pre occlusion pulse signal ratio in the occluded arm, relative to the same ratio in the control (nonoccluded) arm, and corrected for baseline vascular tone. Baseline pulse amplitude and PAT ratio during hyperemia are measures of pressure pulsatility and microvascular function in the finger, respectively. We used Cox proportional hazards regression to relate PAT measures in the fingertip to incident CVD events.

RESULTS: During follow-up (median, 9.2 years; range, 0.04–10.0 years), 270 participants (7%) experienced new-onset CVD events (n=270). In multivariable models adjusted for cardiovascular risk factors, baseline pulse amplitude (hazard ratio [HR] per 1 SD, 1.04 [95% CI, 0.90–1.21]; *P*=0.57) and PAT ratio (HR, 0.95 [95% CI, 0.84–1.08]; *P*=0.43) were not significantly related to incident composite CVD events, including myocardial infarction or heart failure. However, higher PAT ratio (HR, 0.76 [95% CI, 0.61–0.94]; *P*=0.013), but not baseline pulse amplitude (HR, 1.15 [95% CI, 0.89–1.49]; *P*=0.29), was related to lower risk for incident stroke. In a sensitivity analysis by stroke subtype, higher PAT ratio was related to lower risk of incident ischemic stroke events (HR, 0.68 [95% CI, 0.53–0.86]; *P*=0.001).

CONCLUSIONS: Novel digital PAT measures may represent a marker of stroke risk in the community.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: epidemiology ■ hyperemia ■ ischemic stroke ■ myocardial infarction ■ risk factors

Digital peripheral arterial tonometry (PAT) is a noninvasive method to assess endothelial and microvascular function in the finger following reactive hyperemia. In community-based studies, relations between PAT measures and cardiovascular risk factors have been reported.[1–4] Similarly, PAT response was associated with the presence of obstructive and nonobstructive coronary artery disease.[5,6] Additionally, in studies of high-risk

Correspondence to: Leroy L. Cooper, PhD, MPH, Biology Department, Vassar College, 124 Raymond Ave, Box 70, Poughkeepsie, NY 12604. Email lcooper@vassar.edu

This manuscript was sent to Jean-Claude Baron, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.031102.

For Sources of Funding and Disclosures, see page 2871.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
FHS	Framingham Heart Study
FMD	flow-mediated dilation
PAT	peripheral arterial tonometry

patients, PAT was associated with increased risk of adverse cardiovascular disease (CVD) outcomes.[7–13] However, these studies included patients with symptoms of chest pain or established CVD and may not be representative of the general population.

PAT measures may indicate early endothelial and microvascular damage and remodeling, which are important potential targets for prevention of CVD. Prior studies suggest the presence of abnormal endothelial function, including PAT responses in patients who have had strokes or in the presence of cerebrovascular disease.[14–16] Thus, we assessed associations between PAT measures and first-onset major CVD events, including stroke, in a sample of FHS (Framingham Heart Study) participants.

METHODS

The procedure for requesting data from FHS can be found at https://framinghamheartstudy.org/.

Participants

The sample was drawn from the FHS Offspring and Third Generation Cohorts, which have been described.[17,18] During Offspring examination 8 (2005–2008; n=3021) and Generation 3 examination 1 (2002–2005; n=4095), a subset of participants underwent assessment of digital PAT (n=5097), which was successfully performed in 4447 (87.2%) participants. Participants were excluded for the following reasons: age <30 years (n=235), prevalent CVD (n=237), missing risk factor or covariate data (n=96), or no follow-up (n=14). All participants provided written informed consent, and protocols were approved by the Boston University Medical Center Institutional Review Board.

Digital PAT

Digital vascular function was assessed by PAT using a device placed on the index finger of each hand (Endo-PAT2000; Itamar Medical).[2] Baseline (prehyperemic) pulse amplitude was measured from each fingertip for ≥2 minutes. Hyperemia was induced with forearm cuff occlusion for 5 minutes on the experimental arm. The response in the control finger not experiencing hyperemia was used to adjust for systemic effects. Pulse amplitude in both fingers was recorded electronically throughout the study and analyzed by computerized algorithm (Itamar Medical) blinded to clinical data. The PAT ratio (or relative hyperemia index) is the ratio of the post-to-pre occlusion pulse signal in the hyperemic arm versus the nonoccluded arm. Baseline pulse amplitude and PAT ratio during hyperemia are measures of pressure pulsatility and microvascular function in the finger, respectively.

Clinical Evaluation, Definitions, and Outcomes

At the FHS examination, we assessed medical history, physical examination, and electrocardiography.[17] Criteria for diabetes were fasting glucose ≥126 mg/dL (7.0 mmol/L) or treatment with insulin or oral hypoglycemic agent. We measured serum cholesterol levels from a fasting blood test. We calculated body mass index as the ratio of body weight (kilograms) and the square of height (meters). We assessed heart rate and mean arterial pressure during arterial tonometry. We assessed hypertension treatment, lipid disorder treatment, and smoking via questionnaire. We defined smoking as self-reported regular use of cigarettes in the year preceding the examination. Left ventricular hypertrophy on ECG was defined as described previously.[19] To assess the presence of atrial fibrillation, we reviewed all available electrocardiograms from examination cycles, outpatient and inpatient hospital records, or ambulatory ECG monitoring.

Criteria for CVD events have been described previously.[20,21] We defined CVD events as fatal or nonfatal myocardial infarction, unstable angina, heart failure, and ischemic and hemorrhagic stroke. We obtained medical records for hospitalizations and physician visits related to CVD during follow-up. A committee of 3 investigators reviewed these records and adjudicated CVD events following written protocols.

Statistical Analyses

We examined the associations between PAT measures (ie, baseline pulse amplitude and PAT ratio) and the time to incident CVD event using Cox proportional hazards regression. We tested the proportional hazards assumption by assessing the significance of interactions of each PAT measure with survival time. Covariates were selected a priori and included components of the atherosclerotic CVD risk score.[22] We performed natural logarithm transformations of PAT measures to normalize their skewed distributions and limit heteroskedasticity.

We assessed relations between PAT measures and incidence of CVD events (composite events) in models initially adjusted for age, sex, and cohort. We further adjusted multivariable Cox models for standard risk factors (mean arterial pressure, total/high-density lipoprotein cholesterol ratio, smoking, diabetes, and hypertension treatment) and for factors associated with PAT measures (body mass index, heart rate, and lipid disorder treatment).[2] We also assessed relations between PAT measures and incidence of each of the three most common CVD event types—myocardial infarction, heart failure, and stroke (hemorrhagic or ischemic)—separately using multivariable Cox models with similar adjustment. Models for stroke outcomes were further adjusted for known risk factors of stroke: prevalent left ventricular hypertrophy and atrial fibrillation. We calculated the C statistic to assess the incremental prognostic value of the PAT variables when added to a baseline model incorporating measured risk factors. As an alternative method to assess confounding, we estimated the generalized propensity scores by regressing the standardized continuous PAT measures on covariate risk factors.[23,24] We further adjusted significant multivariable models with the generalized propensity scores. As a different approach, we further

assessed confounding using inverse probability weighting. We estimated partial correlations between PAT measures and the Framingham Stroke Risk Score[25] accounting for age and sex. We performed a sensitivity analysis for incident ischemic stroke subtype by excluding incident hemorrhagic stroke events. For PAT measures that showed statistically significant associations with incident CVD events, we examined effect modification by median age and sex by incorporating corresponding interaction terms in the models. To further assess relations between PAT measures and CVD events, continuous PAT predictors were categorized into quartiles, and curves of cumulative probability of a CVD event were constructed. We used Cox models to relate categorized PAT measures to the onset of major CVD adjusting for standard risk factors. Non-CVD death was a censoring event; the curves of cumulative probability were not modified for competing events.

All analyses were performed with SAS, version 9.4, for Windows (SAS Institute, Cary, NC). Two-tailed $P<0.05$ was considered statistically significant except for interaction models where $P<0.1$ was considered statistically significant.

RESULTS

Reporting for this study conforms to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[26] Study exclusion criteria resulted in a sample of 3865 participants (2014 [52.1%] women). Characteristics of the study sample are presented in Table 1; we present a comparison of these characteristics for included versus excluded participants in Table I in the Data Supplement. The excluded participants were similar but included higher proportions of diabetics and individuals using medications for hypertension and lipid disorders.

Table 1. Clinical Characteristics of the Sample (n=3865)

Variable	Value*
Clinical variables	
Age, y	55±14
Women, n (%)	2014 (52.1)
Offspring, n (%)	2187 (56.6)
Body mass index, kg/m^2	27.7±5.4
Heart rate, bpm	61.5±9.8
Mean arterial pressure, mm Hg	95.0±11.8
Total/HDL cholesterol ratio	3.66±1.24
Hypertension treatment, n (%)	1145 (29.6)
Diabetes, n (%)	301 (7.8)
Smoker, n (%)	469 (12.1)
Lipid disorder treatment, n (%)	993 (25.7)
Digital PAT measures	
Baseline pulse amplitude†	5.63±0.89
PAT ratio	0.71±0.41

HDL indicates high-density lipoprotein; and PAT, peripheral arterial tonometry.
*Values are mean±SD except as noted.
†Arbitrary units. Baseline pulse amplitude and PAT ratio were natural logarithm transformed.

Cox proportional hazards models for PAT measures as predictors of an incident CVD event (composite outcome) are presented in Table 2. After minimal adjustment, both baseline pulse amplitude and PAT ratio were associated with incident CVD risk. Upon further adjustment for potential confounders, the aforementioned associations were attenuated (ie, statistically nonsignificant). Table 3 presents Cox proportional hazards models that relate PAT measures to the incidence of myocardial infarction, stroke, and heart failure (separate models for each outcome). After adjusting for potential confounders, higher PAT ratio, but not baseline pulse amplitude, was related to a lower risk of incident stroke. Models that further adjusted for left ventricular hypertrophy and atrial fibrillation were similar (Table II in the Data Supplement). The addition of PAT ratio modestly improved the incremental predictive utility over models incorporating risk factors alone; the model C statistic increased from 0.8349 (risk factors-only model) to 0.8377 (risk factors plus PAT ratio model) for the incident stroke outcome. Models that further considered the generalized propensity score as a covariate in the Cox models were similar (Table III in the Data Supplement). However, when we performed inverse probability weighting, we observed that higher baseline pulse amplitude was associated with higher risk for incident stroke. Neither baseline pulse amplitude nor PAT ratio was related to incident myocardial infarction or heart failure events. We did not observe significant effect modification by age ($P=0.89$) or sex ($P=0.71$) of the relation of PAT ratio with incident stroke events.

In the sensitivity analysis, 76 of the 92 (83%) stroke events were ischemic. After adjusting for age, sex, cohort, body mass index, heart rate, mean arterial pressure, total/high-density lipoprotein cholesterol ratio, smoking, diabetes, lipid disorder treatment, and hypertension treatment, higher PAT ratio was related to a lower risk of incident ischemic stroke events (hazard ratio, 0.68 [95% CI, 0.53–0.86]; $P=0.001$). We did not observe significant effect modification by age ($P=0.46$) or sex ($P=0.89$) of the relation of PAT ratio with incident ischemic stroke events. In partial correlation models that considered age and sex, PAT ratio ($r_p=-0.11$; $P<0.001$) and baseline pulse amplitude ($r_p=0.21$; $P<0.001$) were weakly to modestly correlated with the Framingham Stroke Risk Score.

The Figure depicts the adjusted cumulative probability of incident stroke events grouping participants by quartiles of PAT ratio. In a model adjusted for potential confounders, participants in the highest PAT ratio group (versus participants in the lowest PAT ratio group) had a significantly lower risk of stroke (hazard ratio, 0.43 [95% CI, 0.22–0.86]; $P=0.02$). We present an unadjusted Kaplan-Meier plot for incident stroke by PAT ratio group in Figure I in the Data Supplement. We observed no significant differences between the quartile groups for baseline pulse amplitude and stroke. Figure II in the Data

 Stroke. 2021;52:2866–2873. DOI: 10.1161/STROKEAHA.120.031102

Table 2. PAT Measures as Predictors of Individual Predictors of Incident Composite Cardiovascular Events (n=3865)

PAT measure	Hazard ratio including age, sex, and cohort (LCL–UCL)	*P* value	Hazard ratio including standard risk factors* (LCL–UCL)	*P* value
Baseline pulse amplitude	1.26 (1.10–1.45)	0.001	1.04 (0.90–1.21)	0.57
PAT ratio	0.83 (0.74–0.94)	0.002	0.95 (0.84–1.08)	0.43

Models consider vascular measures individually, one at a time. On the left, all models also include age, sex, and cohort. Hazard ratios expressed per 1-SD higher value. CVD events (n=270 [7%]) were observed over a median 9.2 y of follow-up. LCL indicates lower limit of the 95% CI; PAT, peripheral arterial tonometry; and UCL, upper limit of the 95% CI.

*Models are adjusted for age, sex, cohort, body mass index, heart rate, mean arterial pressure, total/high-density lipoprotein cholesterol ratio, smoking, diabetes, lipid disorder treatment, and hypertension treatment.

Supplement depicts the adjusted cumulative probability of an incident (composite) CVD event when participants were grouped by quartiles of PAT ratio. We observed no significant differences between the quartile groups of either PAT measure and CVD events.

DISCUSSION

Principal Findings

We investigated the relations between PAT measures—baseline pulse amplitude and PAT ratio (measures of pressure pulsatility and microvascular function in the finger, respectively)—and incident CVD events in 2 generations of the community-based FHS. In multivariable models adjusted for potential confounders, neither baseline pulse amplitude nor PAT ratio (relative hyperemia index) was significantly related to incident composite CVD events. However, after assessing risk for individual event outcomes, lower PAT ratio (ie, worse digital microvascular dysfunction) was related to higher stroke risk in multivariable-adjusted models. PAT measures were not significantly related to incident myocardial infarction or heart failure. Thus, our results suggest that PAT ratio may be associated with stroke risk in the community.

PAT Measures and CVD Risk

Novel measures of small vessel and microvascular function are important clinical predictors of CVD risk in the community and have contributed to our understanding of CVD incidence and progression. Ultrasound-based methods to assess macro- and microvascular function have been shown to predict incident CVD. For example, brachial artery flow-mediated dilation (FMD)—a common measure of conduit artery (macrovascular) endothelial function[27]—has been shown to predict incident CVD among high-risk populations.[28,29] However, recent studies in large, community-based cohorts reported that hyperemic flow velocity (an indicator of microvascular function), but not FMD, was a significant predictor for incident cardiovascular events.[30,31] A meta-analysis showed that FMD is associated with composite cardiovascular events that is more robust in patients with established CVD.[32] Thus, noninvasive methods to assess large and small vessel function are important research tools and may be clinically relevant for CVD risk prediction.

In the present study, we performed digital PAT as a noninvasive method to assess microvascular function in the finger following reactive hyperemia. In patients with chest pain, PAT responses have been associated with incident cardiovascular events.[7–9,11] In a meta-analysis of 6 small studies, PAT response remained associated with cardiovascular risk in patients with clinical cardiovascular symptoms or disease.[32] In contrast, PAT measures were not associated with incident composite CVD events in the present community-based sample. The difference from prior studies may represent differences in the associations of the PAT hyperemic response based on the underlying risk of the samples studied (similar to what has been shown for FMD). In addition, the present study has greater ability to account for potential confounding risk factors. Importantly, compared with associations observed in models with limited adjustment, associations between PAT measures and composite CVD events were rendered statistically nonsignificant in multivariable models, suggesting that standard risk factors or pharmacological treatments may account for previously observed associations.

Table 3. PAT Measures as Predictors of Incident Myocardial Infarction, Stroke, and Heart Failure (n=3865)

PAT measure	Hazard ratio (LCL–UCL) for myocardial infarction	*P* value	Hazard ratio (LCL–UCL) for stroke	*P* value	Hazard ratio (LCL–UCL) for heart failure	*P* value
Baseline pulse amplitude	1.34 (0.99–1.79)	0.051	1.15 (0.89–1.49)	0.29	0.99 (0.78–1.26)	0.96
PAT ratio	0.98 (0.77–1.24)	0.85	0.76 (0.61–0.94)	0.01	1.05 (0.86–1.28)	0.63

Models consider vascular measures individually, one at a time. All models were adjusted for age, sex, cohort, body mass index, heart rate, mean arterial pressure, total/high-density lipoprotein cholesterol ratio, smoking, diabetes, lipid disorder treatment, and hypertension treatment. Hazard ratios expressed per 1-SD higher value. We observed 78 myocardial infarction events (2.0%), 92 stroke events (2.4%), and 102 heart failure events (2.7%) over a median of 9.65, 9.41, and 9.34 y of follow-up, respectively. LCL indicates lower limit of the 95% CI; PAT, peripheral arterial tonometry; and UCL, upper limit of the 95% CI.

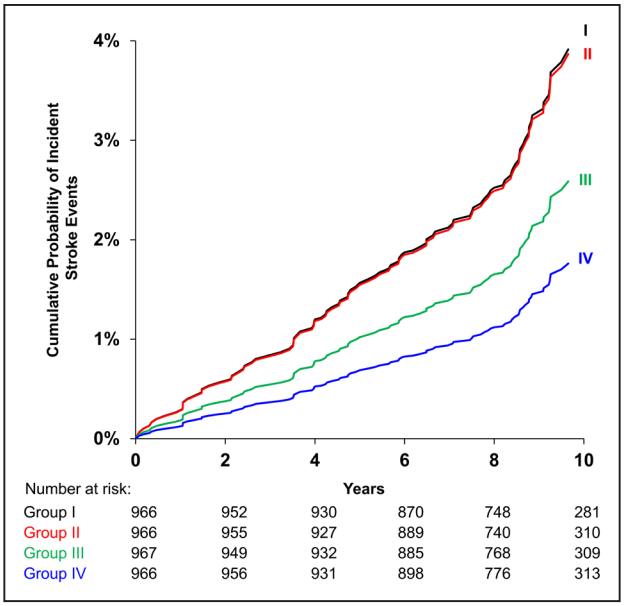

Figure. Adjusted estimators of the cumulative probability of an incident stroke when participants were grouped according to quartiles of peripheral arterial tonometry (PAT) ratio (n=3865).

The probability curves are adjusted for age, sex, cohort, body mass index, heart rate, mean arterial pressure, total/high-density lipoprotein cholesterol ratio, smoking, diabetes, lipid disorder treatment, and hypertension treatment. Group I (≤0.4066; 33/966), group II (>0.4066–0.7258; 30/966), group III (>0.7258–0.9905; 16/967), and group IV (>0.9905; 13/966). Participants in the highest PAT ratio group vs participants in the lowest PAT ratio group had an adjusted hazard ratio of 0.43 ([95% CI, 0.22–0.86]; *P*=0.02).

PAT represents digital microvascular function of the finger, whereas FMD and hyperemic flow velocity assess forearm microvascular response. Therefore, PAT measures may assess a different physiological response to transient ischemia, suggesting a distinct pathological mechanism to cardiovascular risk, and may underlie differential associations with incident composite CVD events compared with measures of endothelial and microvascular dysfunction derived from conduit arteries (ie, FMD and hyperemic flow velocity, respectively). In a few community-based studies, distinct risk factor correlates of PAT measures and FMD have been reported.[1,2,4,33,34] Previously, we reported that the presence of abnormal FMD and hyperemic flow velocity (ie, vascular measures lower than the fifth percentile of a reference sample) were significantly related to standard CVD risk factors, such as higher age and systolic blood pressure, whereas abnormal PAT ratio was more sensitive to metabolic and behavioral risk factors, such as higher body mass index, higher total/HDL (high-density lipoprotein) cholesterol ratio, presence of diabetes and hyperlipidemia, and active smoking.[3] Furthermore, abnormal PAT ratio was not associated with abnormal FMD or hyperemic flow velocity, though each is assessed via the same physiological stimulus (ie, forearm transient ischemia).[3] Therefore, the response to transient ischemia may depend on differential physiological mechanisms and anatomies within and downstream of the brachial artery versus in the finger. For example, contrary to measurements from the brachial artery alone, PAT ratio may incorporate contributions from the digital vascular responses, which have dual circulations and include arteriovenous anastomoses, as well as nutritive vessels. Furthermore, during reactive hyperemia, endothelial-derived NO governs the FMD response[35–38]; however, NO only partially contributes to the PAT ischemic response,[39] which is also regulated by the sympathetic nervous system.[40,41] Thus, PAT ratio may represent a complex response to transient ischemia that involves mechanisms related to both endothelial dysfunction and alterations of autonomic tone. Although further studies are required to assess their relative contributions to indices of microvascular function, several studies suggest significant cross talk between the autonomic nervous system and the endothelium.[42,43]

PAT Ratio and Stroke Risk

Although PAT measures were not related to incident composite CVD events, we observed a significant association between lower PAT ratio and higher risk for incident stroke. A prior cross-sectional study showed lower PAT ratio in patients who had an atherothrombotic compared with cardioembolic stroke.[16] Also, lower FMD has been associated with vascular events in patients with prior stroke.[44] Although stroke has been included in the composite outcome measures of several prior longitudinal studies of FMD and PAT response,[32] stroke was not separated as an individual outcome. Thus, the current finding of an association between PAT response and stroke risk is novel and hypothesis generating.

Multiple potential mechanisms may link microvascular function with stroke risk. The healthy endothelium produces NO in response to vasoactive stimuli in the cerebral microcirculation.[45] Animal studies also show that NO guards against ischemic stroke by increasing collateral flow to ischemic portions of the brain.[46–48] However, lower PAT ratio may be particularly relevant to brain vascular regulation. Since the brain is a high-flow and low-resistance organ, it is particularly sensitive and susceptible to perturbations of the systemic circulation that may affect cerebral blood flow, which may explain why lower PAT ratio was significantly related to incident stroke but not related to other CVD event outcomes. Additional studies that assess putative relations between PAT measures and structural and functional brain indices are warranted.

Furthermore, noninvasive methods to assess large and small vessel function are clinically relevant for CVD risk prediction. Only a few studies have shown vascular measures (eg, coronary artery calcification, carotid intima-media thickness, ambulatory arterial stiffness index, and ankle-brachial index) to predict incident stroke events in the general community,[49–52] but these

 Stroke. 2021;52:2866–2873. DOI: 10.1161/STROKEAHA.120.031102

studies did not consider the contributions of antihypertension and lipid-lowering treatments, which are known to modify vascular function and stroke risk. In addition, current ultrasound-based methods can be technically challenging to acquire and interpret, may be uncomfortable for patients, and require expensive equipment not typically found in physicians' offices. Our study is the first to characterize the extent to which PAT measures are associated with first-onset major CVD events in a community that is at low-to-moderate CVD risk. As a predictor of incident stroke, assessment of PAT ratio may indicate early subclinical cerebrovascular damage and remodeling, atherosclerosis, or autonomic nervous system abnormalities. The PAT measures we present in the current study may assist clinicians in diagnosing and characterizing microvascular dysfunction and aid them in decision-making and treatment planning. Thus, patients with aberrant PAT measurements may require more rigorous medical management of traditional and nontraditional risk factors to improve microvascular function and lower stroke risk. PAT is an attractive point-of-care technique for potential risk stratification: it is relatively easy to perform (eg, the fingers are readily accessible and the technique is automated); intra- and interobserver variability is low (compared with ultrasound techniques); and the extracted PAT measures are highly correlated with invasive measures.[53–55] However, additional studies are needed to determine whether devices that assess digital vascular function potentially have wider utility at the point of care for improved risk stratification.

Limitations

Our study has limitations that should be considered. Although we were able to establish a temporal relation, our prospective study is observational. We cannot dismiss the possibility that there may be residual confounding by unknown or unmeasured risk factors, and we did not perform inverse probability weighting or propensity score matching to test the robustness of our findings. We did not account for multiple statistical testing; thus, our study is more susceptible to type-1 error. In addition, since the low number of incident stroke events reduces the precision of the estimates, an estimation of risk reclassification was not performed. However, PAT ratio is strongly associated with stroke risk but only weakly correlated with the Framingham Stroke Risk Score, suggesting that PAT ratio may add to standard risk prediction models and reclassify stroke risk in a clinically relevant manner. Although we adjusted for lipid disorder and hypertension treatment, medication use may have reduced the number of observed stroke events during the follow-up period. However, we have sufficient statistical power to resolve differences between PAT ratio groups. Since the majority of participants were White individuals of European ancestry, our findings may not be generalizable to other racial or ethnic groups. Given these limitations, our results should be considered hypothesis generating. However, these limitations should be considered along with the strengths of the study. Here, we were able to investigate the relations between novel measures of vascular function using a noninvasive technique in a large, community-based cohort across 2 generations. The participants have high retention rates, which increases the validity of our longitudinal study. FHS has used standardized protocols to adjudicate CVD events that have been applied reliably over several decades and generations of participants.

Conclusions

Although PAT measures were not associated with composite CVD events, lower PAT ratio—a measure of microvascular structure and function in the finger—was associated with greater risk of incident stroke. Thus, greater microvascular dysfunction assessed noninvasively in the finger predicted stroke events in our sample. Our study shows that PAT measures join an increasing body of novel, noninvasive markers of vascular function that may detect subclinical vascular dysfunction; these markers may indicate early targets for prevention, substantially reducing CVD disease burden. However, further studies are needed to evaluate the association of PAT measures with cerebrovascular function and cognition, as well as the feasibility of assessing PAT measures in the clinic.

ARTICLE INFORMATION

Received May 31, 2020; final revision received January 21, 2021; accepted March 29, 2021.

Affiliations

Biology Department, Vassar College, Poughkeepsie, NY (L.L.C.). Biostatistics and Epidemiology Data Analytics Center (N.W.), Department of Biostatistics (A.S.B., M.G.L.), and Department of Epidemiology (E.J.B., R.S.V.), Boston University School of Public Health, MA. Boston University and NHLBI's Framingham Study, MA (A.S.B., J.R.R., H.J.A., E.J.B., M.G.L., R.S.V., S.S.). Department of Neurology (A.S.B., H.J.A.), Cardiology and Preventive Medicine Sections, Department of Medicine (E.J.B., R.S.V.), and Whitaker Cardiovascular Institute (E.J.B., R.S.V., N.M.H.), Boston University School of Medicine, MA. Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (V.-A.L.). Evans Department of Medicine, Boston University School of Medicine, Boston Medical Center, MA (E.J.B., R.S.V., N.M.H.). Cardiovascular Engineering, Inc, Norwood, MA (G.F.M.). Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio (S.S.).

Acknowledgments

From FHS (Framingham Heart Study) of the National Heart, Lung, and Blood Institute of the National Institutes of Health and Boston University School of Medicine.

Sources of Funding

This work was supported by the National Heart, Lung, and Blood Institute FHS (Framingham Heart Study; contract No. N01-HC-25195, HHSN2682015000001I, and 75N92019D00031) and by HL076784, AG028321, HL070100, HL060040, HL080124, HL071039, HL077447, HL107385, HL126136, HL128914, and 2-K24-HL04334. Dr Mitchell was funded by research grants HL094898, DK082447, HL107385, HL104184, and HL126136 from the National Institutes of Health. Dr Benjamin was funded by research grants

2R01HL092577, 1R01HL141434 01A1, 2U54HL120163, 1R01AG066010, HHSN268201500001I, N01-HC 25195, 1R01HL60040, and 1RO1HL70100 from the National Institutes of Health; research grant 18SFRN34110082 from the American Heart Association; and by an unrestricted research grant from Itamar Medical for this project. Dr Cooper is partially funded by grant 2R25HL105400. Dr Hamburg is funded by U54HL120163, AHA 20SRFRN35120118, and R01 HL115391. Dr Seshadri is funded by grant NS017950 from the National Institute of Neurological Disorders and Stroke. Dr Vasan is supported, in part, by the Evans Medical Foundation and the Jay and Louis Coffman Endowment from the Department of Medicine, Boston University School of Medicine. Dr Aparicio is funded by a research supplement AG054076-02S1 from the National Institute on Aging and by the Aram V. Chobanian Assistant Professorship from the Boston University School of Medicine.

Disclosures

Dr Mitchell is the owner of Cardiovascular Engineering, Inc, a company that develops and manufactures devices to measure vascular stiffness; serves as a consultant to and receives honoraria from Novartis, Merck, Bayer, Servier, and Philips; and reports research grants from Novartis. Dr Benjamin received an unrestricted grant from Itamar Medical for this project. In 2008, Itamar Industries (http://www.itamar-medical.com)—the maker of the peripheral arterial tonometry (PAT) device—gave an unrestricted research grant to the Boston University. Dr Benjamin received no personal salary, honoraria, or consulting fees; the grant was to perform analyses of the epidemiology, genetics, and prognosis of PAT. The grant subscribed to the National Heart, Lung, and Blood Institute guidelines for third-party funding (http://www.nhlbi.nih.gov/funding/policies/thirdparty.htm; total cost, $100 000). Itamar also donated the PAT devices to the Boston University FHS (Framingham Heart Study) from 1999 to 2006. The other authors report no conflicts.

Supplemental Materials

Online Tables I–III
Online Figures I and II

REFERENCES

1. McClendon EE, Musani SK, Samdarshi TE, Khaire S, Stokes D, Hamburg NM, Sheffy K, Mitchell GF, Taylor HR, Benjamin EJ, et al. The relation of digital vascular function to cardiovascular risk factors in African-Americans using digital tonometry: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:325.e2–333.e2. doi: 10.1016/j.jash.2017.04.008
2. Hamburg NM, Keyes MJ, Larson MG, Vasan RS, Schnabel R, Pryde MM, Mitchell GF, Sheffy J, Vita JA, Benjamin EJ. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. *Circulation*. 2008;117:2467–2474. doi: 10.1161/CIRCULATIONAHA.107.748574
3. Hamburg NM, Palmisano J, Larson MG, Sullivan LM, Lehman BT, Vasan RS, Levy D, Mitchell GF, Vita JA, Benjamin EJ. Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. *Hypertension*. 2011;57:390–396. doi: 10.1161/HYPERTENSIONAHA.110.160812
4. Schnabel RB, Schulz A, Wild PS, Sinning CR, Wilde S, Eleftheriadis M, Herkenhoff S, Zeller T, Lubos E, Lackner KJ, et al. Noninvasive vascular function measurement in the community: cross-sectional relations and comparison of methods. *Circ Cardiovasc Imaging*. 2011;4:371–380. doi: 10.1161/CIRCIMAGING.110.961557
5. Matsuzawa Y, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Konishi M, Matsubara J, Sumida H, Kaikita K, Kojima S, et al. Digital assessment of endothelial function and ischemic heart disease in women. *J Am Coll Cardiol*. 2010;55:1688–1696. doi: 10.1016/j.jacc.2009.10.073
6. Matsuzawa Y, Li J, Aoki T, Guddeti RR, Kwon TG, Cilluffo R, Widmer RJ, Gulati R, Lennon RJ, Lerman LO, et al. Predictive value of endothelial function by noninvasive peripheral arterial tonometry for coronary artery disease. *Coron Artery Dis*. 2015;26:231–238. doi: 10.1097/MCA.0000000000000208
7. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, Pumper GM, Lerman LO, Lerman A. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J*. 2010;31:1142–1148. doi: 10.1093/eurheartj/ehq010
8. Shechter M, Matetzky S, Prasad M, Goitein O, Goldkorn R, Naroditsky M, Koren-Morag N, Lerman A. Endothelial function predicts 1-year adverse clinical outcome in patients hospitalized in the emergency department chest pain unit. *Int J Cardiol*. 2017;240:14–19. doi: 10.1016/j.ijcard.2017.04.101
9. Ikonomidis I, Kadoglou NN, Tritakis V, Paraskevaidis I, Dimas K, Trivilou P, Papadakis I, Tzortzis S, Triantafyllidi H, Parissis J, et al. Association of Lp-PLA2 with digital reactive hyperemia, coronary flow reserve, carotid atherosclerosis and arterial stiffness in coronary artery disease. *Atherosclerosis*. 2014;234:34–41. doi: 10.1016/j.atherosclerosis.2014.02.004
10. Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, Ohba K, Matsubara J, Maeda H, Horibata Y, et al. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60:1778–1786. doi: 10.1016/j.jacc.2012.07.036
11. Matsuzawa Y, Sugiyama S, Sumida H, Sugamura K, Nozaki T, Ohba K, Matsubara J, Kurokawa H, Fujisue K, Konishi M, et al. Peripheral endothelial function and cardiovascular events in high-risk patients. *J Am Heart Assoc*. 2013;2:e000426. doi: 10.1161/JAHA.113.000426
12. Matsue Y, Suzuki M, Nagahori W, Ohno M, Matsumura A, Hashimoto Y, Yoshida K, Yoshida M. Endothelial dysfunction measured by peripheral arterial tonometry predicts prognosis in patients with heart failure with preserved ejection fraction. *Int J Cardiol*. 2013;168:36–40. doi: 10.1016/j.ijcard.2012.09.021
13. Matsue Y, Yoshida K, Nagahori W, Ohno M, Suzuki M, Matsumura A, Hashimoto Y, Yoshida M. Peripheral microvascular dysfunction predicts residual risk in coronary artery disease patients on statin therapy. *Atherosclerosis*. 2014;232:186–190. doi: 10.1016/j.atherosclerosis.2013.11.038
14. Scherbakov N, Sandek A, Martens-Lobenhoffer J, Kung T, Turhan G, Liman T, Ebinger M, von Haehling S, Bode-Böger SM, Endres M, et al. Endothelial dysfunction of the peripheral vascular bed in the acute phase after ischemic stroke. *Cerebrovasc Dis*. 2012;33:37–46. doi: 10.1159/000332809
15. Rundek T, Hundle R, Ratchford E, Ramas R, Sciacca R, Di Tullio MR, Boden-Albala B, Miyake Y, Elkind MS, Sacco RL, et al. Endothelial dysfunction is associated with carotid plaque: a cross-sectional study from the population based Northern Manhattan Study. *BMC Cardiovasc Disord*. 2006;6:35. doi: 10.1186/1471-2261-6-35
16. Caballero P, Espuela F, Cuenca J, Marrero J, Naranjo I. Endothelial function in stroke subtypes using endopat technology. *J Neurol Res Ther*. 2015;1:1–10.
17. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol*. 1979;110:281–290. doi: 10.1093/oxfordjournals.aje.a112813
18. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol*. 2007;165:1328–1335. doi: 10.1093/aje/kwm021
19. Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation*. 1990;81:815–820. doi: 10.1161/01.cir.81.3.815
20. Kannel WB, Wolf PA, Garrison RJ, eds. Section 34: Some Risk Factors Related to the Annual Incidence of Cardiovascular Disease and Death in Pooled Repeated Biennial Measurements: Framingham Heart Study, 30 Year Follow-Up. Bethesda, MD: U.S. Department of Health and Human Services; 1987.
21. Frankel DS, Vasan RS, D'Agostino RB Sr, Benjamin EJ, Levy D, Wang TJ, Meigs JB. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol*. 2009;53:754–762. doi: 10.1016/j.jacc.2008.07.073
22. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2935–2959. doi: 10.1016/j.jacc.2013.11.005
23. Zhu Y, Coffman DL, Ghosh D. A boosting algorithm for estimating generalized propensity scores with continuous treatments. *J Causal Inference*. 2015;3:25–40. doi: 10.1515/jci-2014-0022
24. Austin PC. Assessing covariate balance when using the generalized propensity score with quantitative or continuous exposures. *Stat Methods Med Res*. 2019;28:1365–1377. doi: 10.1177/0962280218756159
25. Dufouil C, Beiser A, McLure LA, Wolf PA, Tzourio C, Howard VJ, Westwood AJ, Himali JJ, Sullivan L, Aparicio HJ, et al. Revised Framingham Stroke Risk profile to reflect temporal trends. *Circulation*. 2017;135:1145–1159. doi: 10.1161/CIRCULATIONAHA.115.021275
26. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335:806–808. doi: 10.1136/bmj.39335.541782.AD
27. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340:1111–1115. doi: 10.1016/0140-6736(92)93147-f
28. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. *Circulation*. 2007;115:2390–2397. doi: 10.1161/CIRCULATIONAHA.106.678276
29. Huang AL, Silver AE, Shvenke E, Schopfer DW, Jahangir E, Titas MA, Shpilman A, Menzoian JO, Watkins MT, Raffetto JD, et al. Predictive value of reactive hyperemia for cardiovascular events in patients with peripheral arterial disease undergoing vascular surgery. *Arterioscler Thromb Vasc Biol*. 2007;27:2113–2119. doi: 10.1161/ATVBAHA.107.147322
30. Anderson TJ, Charbonneau F, Title LM, Buithieu J, Rose MS, Conradson H, Hildebrand K, Fung M, Verma S, Lonn EM. Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study. *Circulation*. 2011;123:163–169. doi: 10.1161/CIRCULATIONAHA.110.953653
31. Cooper LL, Palmisano JN, Benjamin EJ, Larson MG, Levy D, Vasan RS, Mitchell GF. Microvascular function mediates relations between aortic stiffness and cardiovascular events. *Circ Cardiovasc Imaging*. 2016;9:e004979.
32. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. *J Am Heart Assoc*. 2015;4:e002270.
33. Mulukutla SR, Venkitachalam L, Bambs C, Kip KE, Aiyer A, Marroquin OC, Reis SE. Black race is associated with digital artery endothelial dysfunction: results from the Heart SCORE study. *Eur Heart J*. 2010;31:2808–2815. doi: 10.1093/eurheartj/ehq295
34. Brant LC, Hamburg NM, Barreto SM, Benjamin EJ, Ribeiro AL. Relations of digital vascular function, cardiovascular risk factors, and arterial stiffness: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort study. *J Am Heart Assoc*. 2014;3:e001279. doi: 10.1161/JAHA.114.001279
35. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Lüscher TF. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation*. 1995;91:1314–1319. doi: 10.1161/01.cir.91.5.1314
36. Mullen MJ, Kharbanda RK, Cross J, Donald AE, Taylor M, Vallance P, Deanfield JE, MacAllister RJ. Heterogenous nature of flow-mediated dilatation in human conduit arteries in vivo: relevance to endothelial dysfunction in hypercholesterolemia. *Circ Res*. 2001;88:145–151. doi: 10.1161/01.res.88.2.145
37. Kooijman M, Thijssen DH, de Groot PC, Bleeker MW, van Kuppevelt HJ, Green DJ, Rongen GA, Smits P, Hopman MT. Flow-mediated dilatation in the superficial femoral artery is nitric oxide mediated in humans. *J Physiol*. 2008;586:1137–1145. doi: 10.1113/jphysiol.2007.145722
38. Lieberman EH, Gerhard MD, Uehata A, Selwyn AP, Ganz P, Yeung AC, Creager MA. Flow-induced vasodilation of the human brachial artery is impaired in patients <40 years of age with coronary artery disease. *Am J Cardiol*. 1996;78:1210–1214. doi: 10.1016/s0002-9149(96)00597-8
39. Nohria A, Gerhard-Herman M, Creager MA, Hurley S, Mitra D, Ganz P. Role of nitric oxide in the regulation of digital pulse volume amplitude in humans. *J Appl Physiol (1985)*. 2006;101:545–548. doi: 10.1152/japplphysiol.01285.2005
40. Coffman JD. Effects of endothelium-derived nitric oxide on skin and digital blood flow in humans. *Am J Physiol*. 1994;267(6 pt 2):H2087–H2090. doi: 10.1152/ajpheart.1994.267.6.H2087
41. Noon JP, Haynes WG, Webb DJ, Shore AC. Local inhibition of nitric oxide generation in man reduces blood flow in finger pulp but not in hand dorsum skin. *J Physiol*. 1996;490 (pt 2):501–508. doi: 10.1113/jphysiol.1996.sp021161
42. Sheng Y, Zhu L. The crosstalk between autonomic nervous system and blood vessels. *Int J Physiol Pathophysiol Pharmacol*. 2018;10:17–28.
43. Bumstock G. Non-synaptic transmission at autonomic neuroeffector junctions. *Neurochem Int*. 2008;52:14–25.
44. Santos-García D, Blanco M, Serena J, Rodríguez-Yáñez M, Leira R, Castillo J. Impaired brachial flow-mediated dilation is a predictor of a new-onset vascular event after stroke. *Cerebrovasc Dis*. 2011;32:155–162. doi: 10.1159/000328651
45. Faraci FM, Brian JE Jr. Nitric oxide and the cerebral circulation. *Stroke*. 1994;25:692–703. doi: 10.1161/01.str.25.3.692
46. Huang Z, Huang PL, Ma J, Meng W, Ayata C, Fishman MC, Moskowitz MA. Enlarged infarcts in endothelial nitric oxide synthase knockout mice are attenuated by nitro-L-arginine. *J Cereb Blood Flow Metab*. 1996;16:981–987. doi: 10.1097/00004647-199609000-00023
47. Morikawa E, Moskowitz MA, Huang Z, Yoshida T, Irikura K, Dalkara T. L-arginine infusion promotes nitric oxide-dependent vasodilation, increases regional cerebral blood flow, and reduces infarction volume in the rat. *Stroke*. 1994;25:429–435. doi: 10.1161/01.str.25.2.429
48. Endres M, Laufs U, Huang Z, Nakamura T, Huang P, Moskowitz MA, Liao JK. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci USA*. 1998;95:8880–8885. doi: 10.1073/pnas.95.15.8880
49. Hermann DM, Gronewold J, Lehmann N, Moebus S, Jöckel KH, Bauer M, Erbel R; Heinz Nixdorf Recall Study Investigative Group. Coronary artery calcification is an independent stroke predictor in the general population. *Stroke*. 2013;44:1008–1013. doi: 10.1161/STROKEAHA.111.678078
50. Gronewold J, Hermann DM, Lehmann N, Kröger K, Lauterbach K, Berger K, Weimar C, Kälsch HIM, Moebus S, Jöckel KH, et al; Heinz Nixdorf Recall Study Investigative Group. Ankle-brachial index predicts stroke in the general population in addition to classical risk factors. *Atherosclerosis*. 2014;233:545–550. doi: 10.1016/j.atherosclerosis.2014.01.044
51. Hermann DM, Gronewold J, Lehmann N, Seidel UK, Möhlenkamp S, Weimar C, Kälsch H, Moebus S, Jöckel KH, Erbel R, et al. Intima-media thickness predicts stroke risk in the Heinz Nixdorf Recall study in association with vascular risk factors, age and gender. *Atherosclerosis*. 2012;224:84–89. doi: 10.1016/j.atherosclerosis.2012.06.019
52. Hansen TW, Staessen JA, Torp-Pedersen C, Rasmussen S, Li Y, Dolan E, Thijs L, Wang JG, O'Brien E, Ibsen H, et al. Ambulatory arterial stiffness index predicts stroke in a general population. *J Hypertens*. 2006;24:2247–2253. doi: 10.1097/01.hjh.0000249703.57478.78
53. Woo JS, Jang WS, Kim HS, Lee JH, Choi EY, Kim JB, Kim WS, Kim KS, Kim W. Comparison of peripheral arterial tonometry and flow-mediated vasodilation for assessment of the severity and complexity of coronary artery disease. *Coron Artery Dis*. 2014;25:421–426. doi: 10.1097/MCA.0000000000000094
54. Dhindsa M, Sommerlad SM, DeVan AE, Barnes JN, Sugawara J, Ley O, Tanaka H. Interrelationships among noninvasive measures of postischemic macro- and microvascular reactivity. *J Appl Physiol (1985)*. 2008;105:427–432. doi: 10.1152/japplphysiol.90431.2008
55. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH, Udelson JE. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J*. 2003;146:168–174. doi: 10.1016/S0002-8703(03)00094-2