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Cross-Sectional Relations of Digital Vascular Function to Cardiovascular Risk Factors in the Framingham Heart Study

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Background—Digital pulse amplitude augmentation in response to hyperemia is a novel measure of peripheral vasodilator function that depends partially on endothelium-derived nitric oxide. Baseline digital pulse amplitude reflects local peripheral arterial tone. The relation of digital pulse amplitude and digital hyperemic response to cardiovascular risk factors in the community is unknown.

Methods and Results—Using a fingertip peripheral arterial tonometry (PAT) device, we measured digital pulse amplitude in Framingham Third Generation Cohort participants (n=1957; mean age, 40±9 years; 49% women) at baseline and in 30-second intervals for 4 minutes during reactive hyperemia induced by 5-minute forearm cuff occlusion. To evaluate the vascular response in relation to baseline, adjusting for systemic effects and skewed data, we expressed the hyperemic response (called the PAT ratio) as the natural logarithm of the ratio of postdeflation to baseline pulse amplitude in the hyperemic finger divided by the same ratio in the contralateral finger that served as control. The relation of the PAT ratio to cardiovascular risk factors was strongest in the 90- to 120-second postdeflation interval (overall model $R^2=0.159$). In stepwise multivariable linear regression models, male sex, body mass index, ratio of total to high-density lipoprotein cholesterol, diabetes mellitus, smoking, and lipid-lowering treatment were inversely related to PAT ratio, whereas increasing age was positively related to PAT ratio (all $P<0.01$).

Conclusions—Reactive hyperemia produced a time-dependent increase in fingertip pulse amplitude. Digital vasodilator function is related to multiple traditional and metabolic cardiovascular risk factors. Our findings support further investigations to define the clinical utility and predictive value of digital pulse amplitude. (*Circulation*. 2008;117:2467-2474.)

Key Words: cohort studies ■ epidemiology ■ vasodilation

Endothelial dysfunction is a key component of atherogenesis and contributes to the development of clinical cardiovascular disease.¹ In the presence of vascular risk factors, endothelial cells undergo phenotypic changes resulting in decreased nitric oxide bioactivity, thereby promoting vasoconstriction, inflammation, and thrombosis.² In human studies, risk factors for vascular disease have been associated with impaired vasomotor function, and individuals with abnormal vasodilator function have increased cardiovascular event rates.³

ing as a useful method for assessing vascular function.^{4,5} In response to hyperemic flow, digital pulse amplitude increases, a response that has been shown to depend in part on nitric oxide synthesis.⁶ Augmentation of pulse amplitude in the finger with hyperemia is a complex response to ischemia and reflects both changes in digital flow and digital microvessel dilation. In prior clinical studies, impairment of pulse amplitude hyperemic response was associated with the presence of coronary artery endothelial dysfunction.^{4,7}

Previous studies investigating the relations of digital pulse amplitude to clinical risk factors have been limited to small, selected samples. We sought to evaluate the correlates of digital pulse amplitude responses as a measure of peripheral vascular function in the large, community-based Framingham Heart Study.

Editorial p 2428

Clinical Perspective p 2474

Measurement of peripheral vasodilator response with a fingertip pulse amplitude tonometry (PAT) device is emerg-

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The online-only Data Supplement, which contains a table, can be found with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.748574/DC1>.

Guest Editor for this article was Thomas F. Lüscher, MD.

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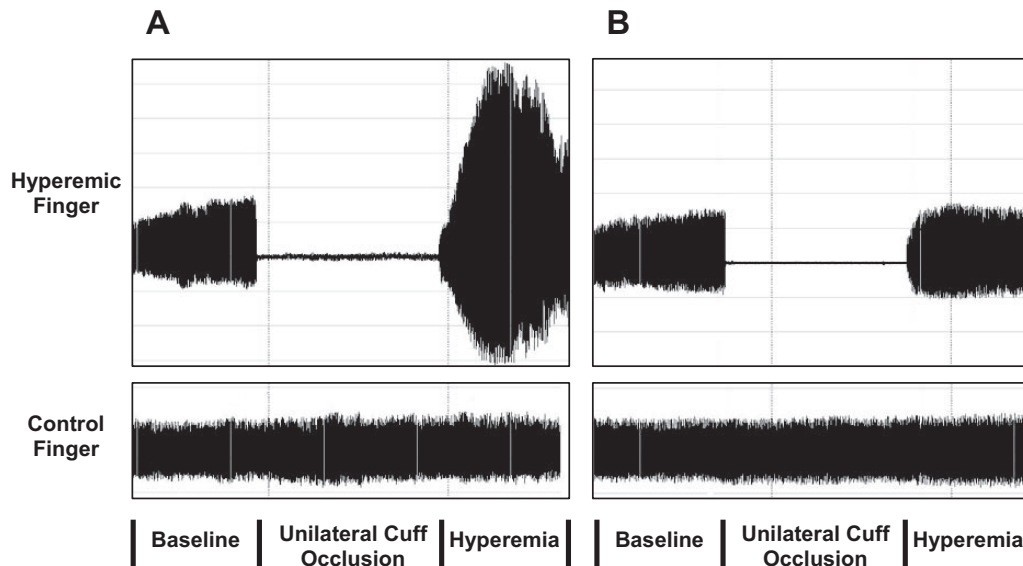


Figure 1. Pulse amplitude tracing in a participant with a PAT ratio in the highest tertile (A) and in a participant with a PAT ratio in the lowest tertile (B). As shown, in the arm undergoing hyperemia (A and B, top tracing), baseline amplitude is recorded; subsequently, during cuff inflation, flow is occluded and rapidly rises after release during the hyperemic period in an individual with a high response (A) but not in an individual with a low response (B). In the contralateral control finger (A and B, bottom tracing), flow continues throughout, and pulse amplitude undergoes minimal change.

Methods

Participants

The design for the Third Generation Cohort has been described elsewhere.⁸ The first examination cycle (2002 to 2005) included 4095 participants.⁸ The acquisition of PAT data began partway through the first examination; therefore, 2217 participants were eligible for participation. Of those eligible for participation, we excluded 260 subjects because of Raynaud's disease (n=2), unavailable finger probe (n=7), patient refusal (n=5), missing data file (n=8), sonographer error (n=1), anatomic issue (mastectomy or arm or hand abnormality; n=13), technically inadequate study (n=207), and missing covariate data (n=17). Technically inadequate studies included those with inadequate flow occlusion (n=73), poor PAT signal quality (n=64), incomplete PAT data acquisition (n=64), and computer error (n=6). Participants who had available PAT data were more likely to be men, smokers, on hypertensive medications, and on lipid-lowering medications and had a higher ratio of total to high-density lipoprotein (HDL) cholesterol (see the Table in the online-only Data Supplement).

All participants underwent routine medical history, physical examination, and laboratory assessment of risk factors and C-reactive protein (CRP). Current cigarette smoking (within the year before examination) was determined by self-report. Waist circumference was measured at the umbilicus level. The Boston University Medical Center Institutional Review Board approved the study, and all participants provided written informed consent.

Determination of Digital Pulse Amplitude

Digital pulse amplitude was measured in the fasting state with a PAT device placed on the tip of each index finger (Endo-PAT2000, Itamar Medical, Caesarea, Israel). The PAT device comprises a pneumatic plethysmograph that applies uniform pressure to the surface of the distal finger, allowing measurement of pulse volume changes in the finger. Throughout the study, the inflation pressure of the digital device was electronically set to 10 mm Hg below diastolic blood pressure or 70 mm Hg (whichever was lower). Baseline pulse amplitude was measured from each fingertip for 2 minutes 20 seconds. Arterial flow was interrupted for 5 minutes by a cuff placed on a proximal forearm (Hokanson AG101, D.E. Hokanson Inc, Bellevue, Was) at whichever occlusion pressure would be higher:

200 mm Hg or 60 mm Hg plus systolic blood pressure. Pulse amplitude was recorded electronically in both fingers and analyzed by a computerized, automated algorithm (Itamar Medical) that provided the average pulse amplitude for each 30-second interval after forearm cuff deflation up to 4 minutes (see the representative tracing in Figure 1).

Statistical Analysis

For each 30-second interval, pulse amplitude response to hyperemia was calculated from the hyperemic fingertip as the ratio of the postdeflation pulse amplitude to the baseline pulse amplitude (ie, X_{ht}/X_{h0} , with X representing pulse amplitude, h denoting hyperemic finger, t denoting time interval, and 0 denoting baseline). We divided this result by the corresponding ratio from the contralateral, control hand (ie, X_{ct}/X_{c0} , with c denoting the control finger, t denoting time interval, and 0 denoting baseline) to obtain the PAT ratio. In scatterplots, the relation between baseline and postdeflation variables was not linear and errors were not homoscedastic; therefore, we used a natural logarithmic transformation of the PAT ratio: $PAT\ ratio = \ln[(X_{ht}/X_{h0})/(X_{ct}/X_{c0})]$.

We tabulated descriptive characteristics separately by sex. We examined age- and sex-adjusted linear regression models to determine the correlates of baseline pulse amplitude and PAT ratio responses with the following clinical covariates: systolic and diastolic blood pressures, heart rate, body mass index, ratio of total to HDL cholesterol, triglycerides, glucose, diabetes mellitus, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease. For each 30-second time interval after cuff release, we examined stepwise selection (with age and sex forced in) to create multivariable models, with the criterion of $P < 0.05$ for a variable to enter and stay in the model. Secondly, we tested potential effect modification by age and sex for covariates retained in the stepwise models. All analyses were performed with SAS 8.1 (SAS Institute Inc, Cary, NC).⁹ Values of 2-sided $P < 0.05$ for primary analyses and $P < 0.01$ for secondary analyses were considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 1. Participant Characteristics

Characteristic	Men (n=1003)	Women (n=954)
Age, y	40±9	40±9
Systolic blood pressure, mm Hg	120±12	113±14
Diastolic blood pressure, mm Hg	78±9	73±9
Heart rate, bpm	61±9	63±9
Body mass index, kg/m ²	27.9±4.7	26.3±6.2
Total cholesterol/HDL	4.4±1.4	3.3±1.1
Triglycerides, mg/dL	136±102	99±71
Fasting glucose, mg/dL	99±18	92±18
Diabetes mellitus, %	4	2
Smoking, %	21	17
Hypertension, %	21	13
Hormone replacement therapy, %	...	4
Hypertension medication, %	11	9
Lipid-lowering medication, %	12	5
Prevalent cardiovascular disease, %	2	1

Continuous variables are given as mean±SD.

Results

Participant Characteristics and PAT

The clinical characteristics of the 1957 study participants (mean age, 40±9 years; 49% women) are shown in Table 1. Baseline pulse amplitude was higher in men than in women (Table 2). As shown in Table 2, baseline pulse amplitude was correlated with PAT ratio in both men and women.

As shown in Figure 2, after forearm cuff deflation, the ratio of the pulse amplitude to baseline rose rapidly in the hyperemic fingertip, with maximal response occurring in the 60- to 90-second postdeflation interval. After forearm cuff deflation in the contralateral arm, a minimal and nonsustained increase in pulse amplitude occurred in the control fingertip.

To determine the relation between the hyperemic response over time after cuff deflation and clinical cardiovascular risk factors, we performed stepwise regression models for the PAT ratio for each 30-second interval with age and sex forced in, selecting from systolic blood pressure, diastolic blood pressure, heart rate, body mass index, ratio of total to HDL cholesterol, triglycerides, glucose, diabetes, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease. As shown in Figure 3, the overall model R^2 (a representation of the proportion of variability in PAT ratio at each time interval that was explained by the regression on the model covariates) was maximized in the 90- to 120-second postdeflation interval. Previous investigators have used the ratio of pulse amplitude for 60 seconds beginning 1 minute after cuff

Table 2. Pulse Amplitude Measures

	Baseline Pulse Amplitude	PAT Ratio	Correlation of Baseline Pulse Amplitude and PAT Ratio <i>r</i>
Men	6.08±0.72	0.58±0.34	-0.67*
Women	5.14±0.76	0.81±0.36	-0.54*

Values are mean±SD.

* $P<0.0001$; PAT measures are natural logarithm transformed.

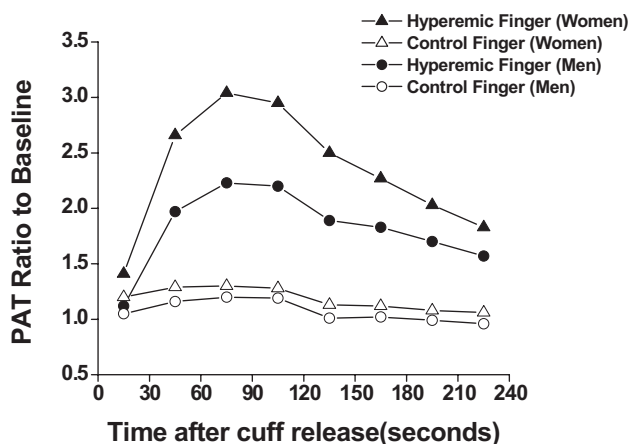


Figure 2. Pulse amplitude response shown for the hyperemic finger and contralateral finger in women and men. Men had lower responses throughout in both fingers. Values are means. The minimum and maximum SEs were 0.01 to 0.04.

release (an average of the 60- to 90-second and 90- to 120-second intervals) to the baseline pulse amplitude divided by the corresponding ratio in the control finger.^{4,7} The overall model R^2 for the mean PAT ratio at 60 to 120 seconds was 0.152, which appeared lower than the model R^2 for the PAT for the 90- to 120-second time interval. Therefore, we selected the 90- to 120-second time interval PAT ratio for subsequent evaluation of the relations between specific risk factors and digital pulse amplitude hyperemic response.

Clinical Correlates of Baseline Pulse Amplitude and Pulse Amplitude Hyperemic Response

In age- and sex-adjusted models, baseline pulse amplitude was directly related to most cardiovascular risk factors, and PAT ratio was inversely associated with most cardiovascular

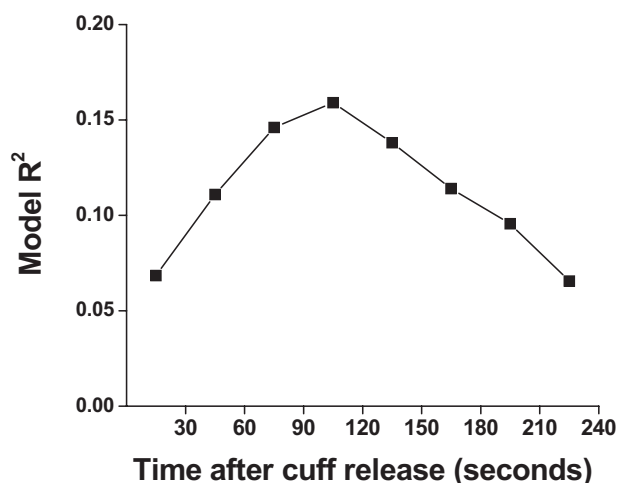


Figure 3. Multivariable relation between cardiovascular risk factors, including age, sex, systolic and diastolic blood pressures, heart rate, body mass index, ratio of total to HDL cholesterol, triglycerides, glucose, diabetes mellitus, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease, and the digital hyperemic response (PAT ratio) in the 30-second time intervals after cuff occlusion. As displayed, the strongest relation occurs in the 90- to 120-second postdeflation interval.

Table 3. Age- and Sex-Adjusted Models of Pulse Amplitude

Characteristic	Mean Baseline		PAT Ratio	
	β (SE)	<i>P</i>	β (SE)	<i>P</i>
Age	0.07 (0.02)	<0.001	0.01 (0.01)	0.55
Sex, female vs male	-0.94 (0.03)	<0.0001	0.24 (0.02)	<0.0001
Systolic blood pressure	0.13 (0.02)	<0.0001	-0.02 (0.01)	0.03
Diastolic blood pressure	0.08 (0.02)	<0.0001	-0.02 (0.01)	0.06
Heart rate	0.05 (0.02)	0.005	-0.04 (0.01)	<0.0001
Body mass index	0.23 (0.02)	<0.0001	-0.06 (0.01)	<0.0001
Total/HDL cholesterol	0.15 (0.02)	<0.0001	-0.06 (0.01)	<0.0001
Triglycerides	0.13 (0.02)	<0.0001	-0.05 (0.01)	<0.0001
Fasting glucose	0.11 (0.02)	<0.0001	-0.04 (0.01)	<0.0001
Diabetes mellitus	0.52 (0.10)	<0.0001	-0.24 (0.05)	<0.0001
Smoking	0.28 (0.04)	<0.0001	-0.09 (0.02)	<0.0001
Hypertension	0.29 (0.05)	<0.0001	-0.08 (0.02)	<0.001
Hormone replacement therapy	0.17 (0.12)	0.15	-0.07 (0.06)	0.21
Hypertension treatment	0.29 (0.06)	<0.0001	-0.11 (0.03)	<0.0001
Lipid-lowering treatment	0.30 (0.06)	<0.0001	-0.14 (0.03)	<0.0001
Prevalent cardiovascular disease	0.22 (0.13)	0.10	-0.03 (0.06)	0.62

The first 2 rows present models for age and sex separately, with no adjustment for the other variable. All continuous variables were standardized to a mean of 0 and an SD of 1; all dichotomous variables were coded 1=presence and 0=absence of the factor.

disease risk factors (Table 3). In stepwise multivariable regression models, the factors inversely associated with PAT ratio were male sex, body mass index, ratio of total to HDL cholesterol, diabetes mellitus, smoking, and lipid-lowering treatment, whereas advancing age was associated with higher mean PAT ratio (Table 4). The overall model explained 15.9% of the variability in PAT ratio. The correlates of increasing baseline pulse amplitude were systolic blood pressure, body mass index, ratio of total to HDL cholesterol, smoking, and lipid-lowering treatment. Female sex and diastolic blood pressure were associated with lower baseline pulse amplitude.

Secondary Analyses

Obesity and Baseline Pulse Amplitude and Pulse Amplitude Hyperemic Response

As displayed in Figure 4, a significant increase in mean age-adjusted PAT ratio with increasing weight category (trend test of normal, overweight, obese, $P<0.0001$) was found in both men and women.

To evaluate the role of abdominal obesity in the relation between obesity and digital vascular function, we assessed the relation of waist circumference to the PAT measures. In age- and sex-adjusted analyses, increasing waist circumference was related to higher baseline pulse amplitude ($\beta=0.23$;

Table 4. Stepwise Models of Baseline and Hyperemic Digital PAT

Characteristic	Mean Baseline			PAT Ratio		
	β (SE)	Partial R^2	<i>P</i>	β (SE)	Partial R^2	<i>P</i>
Age	0.002 (0.017)	0.000	0.90	0.03 (0.01)	0.005	0.001
Sex, female vs male	-0.79 (0.03)	0.161	<0.0001	0.18 (0.02)	0.049	<0.0001
Systolic blood pressure	0.09 (0.02)	0.004	<0.001
Diastolic blood pressure	-0.05 (0.02)	0.002	0.03
Body mass index	0.19 (0.02)	0.037	<0.0001	-0.04 (0.01)	0.011	<0.0001
Total/HDL cholesterol	0.07 (0.02)	0.004	<0.001	-0.04 (0.01)	0.009	<0.0001
Diabetes mellitus	-0.13 (0.05)	0.004	0.004
Smoking	0.26 (0.04)	0.013	<0.0001	-0.08 (0.02)	0.007	<0.0001
Lipid-lowering treatment	0.21 (0.06)	0.004	<0.001	-0.10 (0.03)	0.005	0.0008
Model R^2	...	0.387	0.159	...

Age and sex were forced into all models. Variables allowed to enter into stepwise regression models were systolic and diastolic blood pressures, heart rate, body mass index, ratio of total to HDL cholesterol, triglycerides, glucose, diabetes mellitus, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease. All continuous variables were standardized to a mean of 0 and an SD of 1; all dichotomous variables were coded 1=presence and 0=absence of the factor.

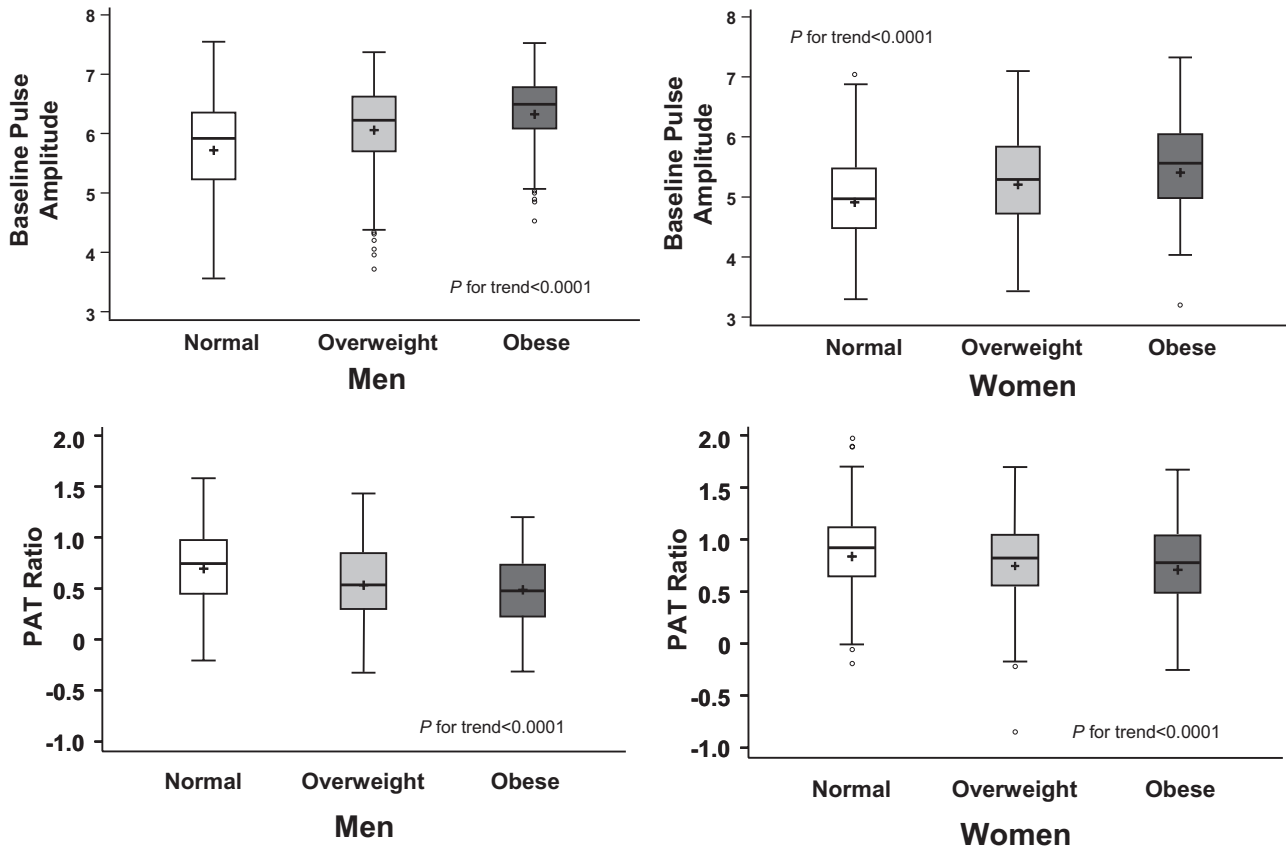


Figure 4. Box plot of age-adjusted baseline and hyperemic pulse amplitude according to body mass index category (normal, <25 kg/m²; overweight, 25 to <30 kg/m²; obese ≥30 kg/m²) and sex. For men, n=283, n=471, and n=249, and for women, n=501, n=253, and n=200 for normal, overweight, and obese, respectively (P for trend <0.0001).

SE, 0.02; P <0.0001) and to lower PAT ratio (β =−0.07; SE, 0.01; P <0.0001). Waist circumference did not enter the stepwise multivariable model relating cardiovascular risk factors to baseline pulse amplitude or to PAT ratio.

Inflammation and Baseline Pulse Amplitude and Pulse Amplitude Hyperemic Response

To explore the possibility that systemic inflammation may adversely affect digital vascular function, we examined the relation of CRP to PAT measures. Overall, the mean CRP was 2.5 ± 4.6 mg/L. Because of a skewed distribution, CRP was log transformed for analysis. In age- and sex-adjusted analyses, a trend was present toward a direct relation between CRP and baseline pulse amplitude (β =0.02; SE, 0.01; P =0.09). In age- and sex-adjusted analyses, no significant relation existed between CRP and PAT ratio (β =−0.006; SE, 0.006; P =0.36). CRP did not enter the stepwise multivariable model relating cardiovascular risk factors to baseline pulse amplitude or to PAT ratio.

Interactions

In multivariable models, for PAT ratio, we observed an interaction between sex and body mass index (P <0.01); the body mass index–estimated effect size was −0.07 for men and −0.03 for women, confirming that the obesity-related decrease in PAT ratio was greater in men than women (Figure 4). In multivariable models, for baseline pulse amplitude, significant interactions were noted between sex and body

mass index and between sex and ratio of total to HDL cholesterol (both P <0.01); for body mass index, the increase was greater in men than women (0.27 in men and 0.14 in women), whereas for the ratio of total to HDL cholesterol, the increase was greater in women than in men (0.02 in men and 0.15 in women).

The prespecified interaction tests between age and the clinical covariates for baseline and PAT ratio were not significant, and no significant relation existed between age and PAT ratio in sex-adjusted models. However, in the multivariable model, we observed an unanticipated positive relation between age and PAT ratios. We examined the step-by-step details of the stepwise regression analysis to reveal which covariate(s) uncovered a positive relation between age and PAT ratio. With age and sex forced in, the first selected covariate was body mass index, revealing a significant positive association between age and PAT ratio (P =0.036). Age was positively correlated with body mass index after adjustment for sex (partial r =0.176, P <0.0001), suggesting negative confounding between age- and sex-adjusted PAT ratio.

Discussion

In our large, community-based cohort, we evaluated the relations of baseline digital pulse amplitude and digital pulse amplitude hyperemic response, a noninvasive measure of peripheral vascular function, to clinical cardiovascular risk

factors. We observed a time-dependent increase in fingertip pulse amplitude that peaked in the 60- to 90-second interval after induction of reactive hyperemia. To identify the most clinically relevant portion of the response, we related the pulse amplitude increase during each 30-second interval to a multivariable risk factor model and observed that the relation was maximized in the interval 90 to 120 seconds after cuff release. We observed that digital pulse amplitude hyperemic response was higher in women than in men and with advancing age and was inversely related to multiple risk factors, particularly diabetes mellitus, body mass index, higher cholesterol concentrations, and smoking. Digital vasodilator function was lower with increasing weight category. Baseline pulse amplitude was higher in men than in women and was directly related to several cardiovascular risk factors.

Prior studies support the use of digital PAT as a measure of peripheral vasomotor function. Nitric oxide has been shown to be an important contributor to the augmentation in fingertip pulse amplitude after ischemia; administration of an endothelial nitric oxide synthase inhibitor blunted the PAT hyperemic response.⁶ Previous investigators also have demonstrated a correlation between the degree of hyperemic response in the fingertip and measures of endothelial vasomotor function. In patients referred for chest pain evaluation, PAT hyperemic response correlated with flow-mediated dilation in the conduit brachial artery and with overall vascular risk factor burden.⁴ In addition, Bonetti et al⁷ reported that reduced PAT hyperemic response predicted the presence of abnormal coronary artery endothelial function in 94 patients undergoing cardiac catheterization. However, in the Bonetti et al study, no correlations were found between individual cardiovascular risk factors and PAT hyperemic response in a multivariable model. An improvement in PAT hyperemic response also has been observed after treatments that are potentially beneficial for cardiovascular health.^{10,11}

In the present study, we extended prior work by comprehensively examining the relations between specific cardiovascular risk factors and the time course of the PAT hyperemic response in a large, community-based cohort. Our observations indicate that the relation between cardiovascular risk factors and PAT hyperemic response was strongest in the 90- to 120-second interval after fingertip flow was restored. The logarithmic transformation of the PAT ratio and selection of the 90- to 120-second time interval increased the overall association with risk factors, suggesting that this may be the optimal method for assessing the PAT response to hyperemia. The selected time period includes the portion of hyperemic response that has previously been shown to depend in part on nitric oxide. Further studies are needed to evaluate the possibility that risk factors impair the PAT hyperemic response by decreasing endothelial nitric oxide bioavailability.⁶

As has been seen with other methods for assessing vasomotor function, we observed expected relations between hyperemic PAT response and a number of classic cardiovascular risk factors. For example, men had a lower PAT hyperemic response than women, which may be related to sex-specific determinants of endothelial function or alternatively to the presence of higher baseline pulse amplitude in men compared with women. The unexpected inverse relation

between lipid-lowering therapy and digital vasodilation is analogous to reports of flow-mediated dilation¹² and is likely attributable to indication bias in our observational, cross-sectional analysis. We speculate that individuals with more severe hyperlipidemia and higher risk factor burden were placed on drug treatment.

Our findings highlight metabolic risk factors, including obesity, diabetes mellitus, and ratio of total to HDL cholesterol, as important correlates of digital vasodilator function. Previous studies have established a relation between metabolic risk factors and vascular dysfunction. Obese animals have an impaired hyperemic response attributable to both decreased microvessel distensibility and microvascular structural remodeling that occur in the setting of heightened oxidant stress and reduced endothelium-derived nitric oxide.^{13–15} In human participants, obesity and diabetes mellitus, along with the associated dyslipidemia and insulin resistance, have been linked to impaired vasodilator responses.^{16–19} The lower digital hyperemic response in obese participants is consistent with impaired microvessel flow reserve, which may contribute to impaired blood flow supply in the setting of increased metabolic demands.¹⁹ Although we did not find a relation between abdominal obesity, reflected in waist circumference, and digital vascular function, it remains possible that a more detailed characterization of fat distribution would provide additional mechanistic understanding of the effect of obesity on microvessel function.

Several traditional risk factors were not related to the PAT hyperemic response. In contrast to studies using alternative methods to evaluate peripheral vasomotor function, no significant relation existed between hypertension and digital vasodilation.¹² Systolic blood pressure was marginally associated with lower PAT hyperemic response in age- and sex-adjusted analysis but not in the multivariable analysis. It is possible that systemic blood pressure has limited effects on the distal microcirculation; however, this finding also could be explained by the low prevalence of hypertension in the relatively young Third Generation Cohort or the use of antihypertensive agents. Blood pressure also may have a predominant influence on the baseline amplitude without additional modification of the hyperemic response when represented as a ratio of hyperemic to baseline amplitude.

Because previous studies have suggested an association between inflammation and vascular dysfunction, we considered the possibility that systemic inflammation may be related to the PAT measures.²⁰ However, we did not observe a relation between systemic inflammation assessed by CRP levels and digital vascular function. These findings suggest that inflammation may not play an important role in determining vasodilator function in the finger in a young to middle-aged cohort. However, it remains possible that local microvessel inflammation not reflected in a circulating marker may influence digital vascular function.

We observed a minimal but paradoxically positive relation between advancing age and PAT hyperemic response. One possible explanation for the counterintuitive positive association with advancing age may be the relatively narrow age range of the participants in this study sample. Alternatively, there may be differential age-related changes in hyperemic

response in the fingertip microvessels compared with other vascular beds. Exploratory analyses suggest that the lack of association between age and PAT ratio in the sex-adjusted model may reflect negative confounding by body mass index and other covariates. The age and PAT ratio association will need to be examined in additional cohorts with broader age distributions. The differences between our findings in the fingertip and previous findings in conduit vessels emphasize that arterial physiology and mechanisms of vasodilation may differ importantly according to vascular bed and the stimulus for vasodilation and may have implications for the clinical utility of the readily accessible digital circulation.

Baseline pulse amplitude was directly related to multiple cardiovascular risk factors. In multivariable analyses, male sex and higher body mass index were strongly related to elevated pulse amplitude at baseline, whereas modest positive relations were observed with increasing systolic blood pressure, increasing ratio of total to HDL cholesterol, and active smoking. Higher baseline pulse amplitude was observed in obese and overweight individuals compared with those of normal weight. Decreased digital microvessel tone, increased pulse pressure, increased blood flow, and altered microvascular structure may all contribute to higher resting pulse amplitude. Baseline pulse amplitude is highly dependent on digital blood flow and sympathetic tone, as is evidenced by a marked reduction in digital pulse amplitude after the administration of phenylephrine, an α -adrenergic vasoconstrictor agent.⁶ Our findings are consistent with the observation that both obesity and smoking are associated with higher resting blood flow in the brachial artery.¹⁹ Similarly, increased peripheral blood flow occurs with acute elevation in circulating free fatty acid levels after ingestion of a fatty meal.²¹ The presence of increased basal blood flow is consistent with the presence of hyperperfusion, which may contribute to microvascular hypertension and microvessel damage in obese individuals.^{19,22,23}

Study Strengths and Limitations

The present study has several limitations. Because of the cross-sectional design, we cannot establish causal relations between risk factors and digital vascular function; however, our findings support the possibility of a link between certain risk factors and lower digital hyperemic response. We acknowledge that much of the variability in pulse amplitude remains unexplained by clinical factors. Because of the large sample size, many of the cardiovascular risk factors were significantly associated with PAT measures but provided only minimal incremental contribution to the variability in pulse amplitude after accounting for age and sex. Because our study sample was predominantly white individuals of European descent, our findings cannot be readily generalized to different ethnic or racial groups. As would be anticipated, we observed an inverse relation between baseline pulse amplitude and the PAT response to hyperemia. Expressing the hyperemic response as a ratio to the baseline pulse amplitude accounts in part for this association. Because of the community-based nature of our cohort, we were unable to administer nitroglycerin; therefore, we do not have a measure of endothelium-independent vasodilation. Thus, we acknowl-

edge that we are unable to comment directly on the relative proportion of the PAT response to ischemia that is endothelium dependent. Our study has several strengths that counterbalance these limitations, including a large sample size and community-based design that reduced selection biases. The standardized evaluation of cardiovascular risk factors in a large number of individuals allowed evaluation of multiple covariates and provided excellent power.

Conclusions

Digital vascular dysfunction, as assessed by the pulse amplitude hyperemic response, occurs in association with multiple cardiovascular risk factors, in particular obesity and associated metabolic risk factors. The association between cardiovascular risk factors and digital arterial tonometry assessed by the PAT ratio suggests that PAT may be a useful measure of peripheral vascular function. The association with obesity and diabetes supports the possibility that metabolic risk factors in particular are reflected in microvessel responses. Future longitudinal studies are warranted to provide additional information about the clinical utility of measuring vasodilator function in the fingertip and the pathways connecting vascular dysfunction, metabolic risk, and cardiovascular disease.

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Disclosures

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CLINICAL PERSPECTIVE

Endothelial dysfunction contributes to atherogenesis and the development of clinical cardiovascular disease. Digital pulse amplitude response to hyperemia is a novel method for noninvasively assessing vascular function in humans. In a large, community-based sample, we measured digital vascular function using a fingertip peripheral arterial tonometry device. Hyperemia produced a time-dependent increase in fingertip pulse amplitude. We related digital vascular response to hyperemia to cardiovascular risk factors. We observed that male sex, body mass index, ratio of total to high-density lipoprotein cholesterol, diabetes mellitus, smoking, and lipid-lowering treatment were associated with lower pulse amplitude hyperemic response. Digital vascular function was related to multiple traditional and metabolic cardiovascular risk factors. Our findings support further studies to define the clinical utility and predictive value of digital pulse amplitude.