Assessment of Endothelial Function Using Digital Pulse Amplitude Tonometry☆,☆☆

Naomi M. Hamburg*, Emelia J. Benjamin

The importance of endothelial dysfunction in the development and clinical expression of cardiovascular disease is well recognized. Impaired endothelial function has been associated with an increased risk of cardiovascular events. Endothelial function may be evaluated in humans by assessing vasodilation in response to stimuli known to induce the release of nitric oxide. A novel pulse amplitude tonometry device noninvasively measures vasodilator function in the microcirculation of the finger. This article reviews the recent studies that support the utility of digital pulse amplitude tonometry as a relevant test of peripheral endothelial function. (Trends Cardiovasc Med 2009;19:6–11) © *2009, Elsevier Inc.*

• Introduction

The significance of endothelial dysfunction in cardiovascular disease is well established (Widlansky et al. 2003). In the healthy state, the endothelium produces a number of factors including nitric oxide that are essential for maintaining vascular homeostasis. Systemic risk factors damage endothelial cells lowering nitric oxide (NO) bioavailability. Endothelial dysfunction facilitates atherogenesis by promoting inflammation, thrombosis and cellular adhesion. Recent studies demonstrate higher risk of cardiovascular events in individuals with impaired endothelial function (Yeboah et al. 2007).

Since the initial identification of NO, several techniques have been employed to investigate endothelial vasomotor function in humans (McMackin and Vita 2005). Endothelial function assessment has not yet been incorporated into routine risk stratification in part owing to technical and logistical limitations. The use of a novel digital pulse amplitude tonometry (PAT) device to measure endothelial function offers the possibility of an easily performed, rapid assessment of vascular function (Celermajer 2008). The current article reviews the use of digital PAT as an indicator of endothelial function.

• Testing of Endothelial Function in Cardiovascular Disease

Endothelial health can be assessed by measuring vasodilator responses to interventions known to stimulate endothelial release of NO. Endothelial function testing has many potential applications in both research and clinical practice that are outlined in Table 1. Several methodologies have been developed to measure endothelial vasomotor function in humans, and these have been the subject of recent reviews (Barac et al. 2007, Deanfield et al. 2007, McMackin and Vita 2005).

The most frequently employed noninvasive endothelial function test is flow-mediated vasodilation of the brachial artery assessed with ultrasound. Brachial artery flow-mediated vasodilation is lower in the presence of traditional risk factors and importantly predicts risk for cardiovascular events (Widlansky et al. 2003, Yeboah et al. 2007). Several limitations have precluded the clinical adoption of brachial ultrasound based testing of endothelial function. In particular, the accurate measurement of brachial flow-mediated vasodilation requires extensive sonographer training, expensive equipment, and labor intensive image analysis. In response to these limitations, investigators have developed new methodologies designed to be simple to perform. The ideal test for endothelial function would satisfy a number of important criteria as outlined in Table 1.

• Measurement of Endothelial Function with the Use of Digital PAT

Emerging evidence supports the assessment of digital PAT as a measure of endothelial function. Assessment of vascular function with PAT involves measuring pulse amplitude in the fingertip at rest and following the induction of reactive hyperemia. The EndoPAT device (Itamar Medical, Caesarea, Israel) is a Federal Drug Administration–approved, commercially available system, consisting of a fingertip plethysmograph capable of sensing volume changes in the digit with each arterial pulsation. The device used to measure digital vascular function is shown in Figure 1. The fingertip probe has a rigid external casing containing inflatable chambers.

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☆ Dr Hamburg is supported by National Institutes of Health grant HL083781. Dr Benjamin receives support from RO1 HL076784, 1R01 AG028321, RO1 HL70100, and N01-HC 25195.

☆☆ Dr Benjamin has received an unrestricted research grant from Itamar Medical (Caesarea, Israel), the manufacturer of the PAT device.

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Table 1. Noninvasive endothelial function testing in practice

Potential utility of endothelial function testing
Discover novel cardiovascular risk factors
Risk-stratify before onset of clinical cardiovascular disease
Risk-stratify in patients with established cardiovascular disease
Predict clinical response to therapy
Investigate disease mechanisms in humans
Criteria to evaluate a test of endothelial function
Relevant biological mechanism
Ease of use: transportable, limited training time, short test duration
Reproducible: across patient groups, locations, and time
Available population reference data on test distribution
Improves on current risk stratification tools:
Acceptable discrimination, calibration, reclassification
Responds to therapeutic interventions
Improvement corresponds to reduced cardiovascular risk

The uniform applied pressure field across the finger prevents venous pooling and partially unloads arterial wall tension. Volume changes in the fingertip are recorded digitally as pulse amplitude that can be tracked over time.

A complete digital PAT endothelial function test includes three phases: baseline, occlusion, and hyperemia. A PAT probe is positioned on one finger of each hand and set by the computer to inflate to 10 mm Hg below diastolic pressure or 70 mm Hg (the lower value is selected). Recordings are taken simultaneously from both fingers throughout the study. The response in the control finger not experiencing hyperemia can be used to adjust for systemic effects. After baseline data acquisition, a blood pressure cuff is inflated on one arm to suprasystolic pressures for 5 minutes. During the occlusion period, signals are absent from the hyperemic finger but continue from the control finger. After cuff release, pulse amplitude increases in the hyperemic finger. The pulse amplitude recordings are digitized and analyzed by an automated, proprietary algorithm. Average pulse amplitude is calculated for each 30-second intervals after cuff occlusion for up to 5 minutes. The baseline pulse amplitude also is measured and reported in standardized, arbitrary units. Figure 2 displays representative recordings from two individuals, one with high and one with low PAT hyperemic response.

The automated assessment of vascular function with PAT produces reliable results. In more than 2,000 eligible participants in the Framingham Heart Study, the rate of technically interpretable studies was over 90% (Hamburg et al. 2008). The major reasons for technical inadequacy were incomplete cuff occlusion (3%), noisy signal quality (3%) and incomplete data acquisition (3%). A few patient-specific factors limit test performance, including Raynaud's disease, a finger size that does not match the fingertip probe, and a very long fingernail. Owing to computerized analysis approach, interobserver measurement variability is minimized. The published data regarding the reproducibility of the digital vascular responses over time are limited. In two small studies of healthy adults, there was evidence supporting the reproducibility of the PAT hyperemic ratio measured on two days (Bonetti et al. 2003, Tomfohr et al. 2008). In 44 children with diabetes, the mean coefficient of variation for the PAT hyperemic response measured 4 weeks apart was 14.8 % (Haller et al. 2007).

We recently reported the characteristics of the PAT hyperemic response in participants in the Third Generation cohort of the Framingham Heart Study (Hamburg et al. 2008). In the hyperemic finger, there was a time-dependent rise in pulse amplitude that on average peaked at 60 to 120 seconds following cuff release. Notably, pulse amplitude increased modestly in the control finger, indicative of a systemic response to cuff occlusion. Owing to the presence of a systemic effect, a measure of the PAT hyperemic response was developed that incorporated the observed changes in the control finger. The PAT ratio was calculated in three steps. First, the ratio of the pulse amplitude in each 30-

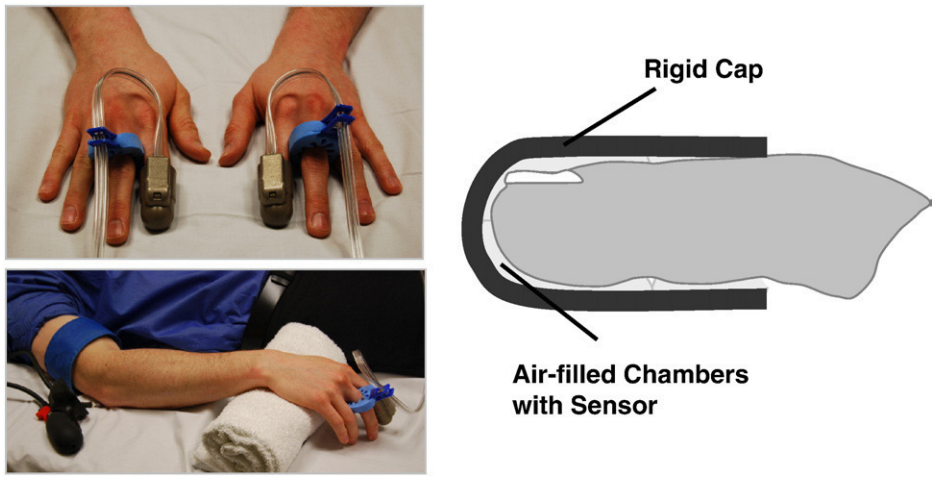

Figure 1. (**Top left**) The thimble-like PAT device is placed on a finger from each hand. Tubing connects the device to a recording unit that transmits data directly to a computer. (**Right**) The device contains air-filled chambers that are inflated to approximate diastolic pressure throughout the study. Sensors allow detection of changes in finger volume with each arterial pulsation. (**Bottom left**) A typical setup for a research study is shown. The hand is elevated to allow the fingers to hang freely without touching any surfaces. A cuff is placed on one forearm that will be inflated to suprasystolic pressures to induce hyperemia.

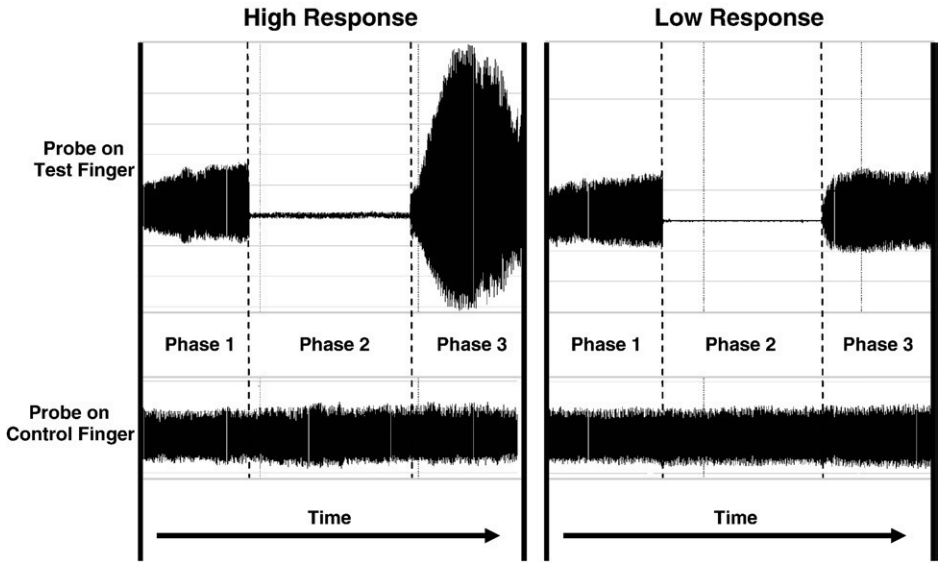

Figure 2. As shown, the tracings on the left are from an individual with a high PAT hyperemic response whereas the tracings on the right are from an individual with a low PAT hyperemic response. The study has three phases. Phase 1 records the baseline pulse amplitude from the probes on both fingers. Phase 2 is during the cuff inflation on one arm. In the test finger flow is occluded but continues in the control finger. Phase 3 is recorded after cuff release. In the test finger, pulse amplitude rises rapidly in the healthy individual but not in the patient with coronary artery disease. In the control finger, flow there is minimal change in pulse amplitude after cuff release.

second interval following cuff release to the baseline pulse amplitude was calculated for the hyperemic finger. Second, this ratio in the hyperemic finger was divided by the corresponding ratio in the control finger. Third, because the PAT ratio was not normally distributed and the error structure was heteroscedastic, we performed a natural logarithm transformation to arrive at the final PAT ratio.

The PAT ratio can be derived for each 30 seconds interval following cuff release. The portion of the PAT hyperemic response shown to be dependent on endothelial NO release occurs from 60 to 120 seconds following cuff deflation (Nohria et al. 2006). Notably, the relation between cardiovascular risk factors and the PAT hyperemic response was maximized in the 90- to 120-second time interval (Hamburg et al. 2008). These findings support selecting the PAT hyperemic response recorded between one and 2 minutes after cuff deflation as the appropriate measure of digital vascular function.

The augmentation of pulse amplitude with hyperemia reflects a complex vascular response to ischemia in the digit (Mitchell et al. 2004). As the PAT device records pulse amplitude in the finger, changes in the PAT signal reflect, in part, vasodilator function of the digital microcirculation. Importantly, NO production by the endothelium has been shown to contribute to the PAT hyperemic response. In healthy volunteers, infusion of an endothelial NO synthase (eNOS) inhibitor blunted the rise in pulse amplitude measured in the minute following cuff release (Nohria et al. 2006). These findings suggest that the increase in digital pulse amplitude that occurs with hyperemia is dependent in part on flow-mediated release of NO and support the use of the PAT hyperemic response as a measure of endothelial function.

- **Clinical Studies Measuring Endothelial Function with Digital PAT**

Investigators have developed evidence supporting the clinical relevance of the PAT hyperemic response. Selected studies measuring PAT hyperemic responses are summarized in Table 2. Multiple studies have examined the relation of PAT hyperemia to established measures of endothelial function. In addition, studies have examined the associations between traditional and novel cardiovascular risk factors and digital vascular function. Finally, investigators have measured the changes in the PAT hyperemic response after short-term interventions.

Several studies have investigated the relation between vascular function in the digit and other regions. In patients undergoing coronary angiography, lower PAT hyperemic response was associated with the presence of coronary endothelial dysfunction measured by acetylcholine response (Bonetti et al. 2004). Two studies reported a modest relation between PAT hyperemic response and brachial flow-mediated dilation (Dhindsa et al. 2008, Kuvin et al. 2003). Thus, in small studies, digital vascular function appears to be associated with endothelial function in the brachial artery. However, the PAT hyperemic response largely reflects vasodilator responses in digital microvessels, whereas brachial artery flow-mediated dilation measures conduit artery vasodilation. Microvascular function as assessed by PAT has the potential to evaluate a distinct vascular response from conduit vessel flow-mediated dilation.

Several studies have examined the relation of clinical cardiovascular risk factors with the PAT hyperemic response. Kuvin et al. (2003) reported that the PAT hyperemic ratio was progressively lower with increasing burden of cardiovascular risk factors. In patients without obstructive coronary artery disease undergoing coronary angiography, increasing body mass index and decreasing high-density lipoprotein (HDL) were associated with lower PAT hyperemic response in unadjusted analyses (Bonetti et al. 2004). Adolescents with type 1 diabetes mellitus also had lower hyperemic PAT responses compared to their healthy peers (Haller et al. 2007, Mahmud et al. 2008).

Several emerging cardiovascular risk factors have been linked to impaired

Table 2. Selected studies of digital pulse amplitude tonometry hyperemic response

Reference	*Study population*	*Study details*	*Main findings*
Observational			
Community-based			
Dhindsa et al (2008)	40 healthy adults	PAT, FMD, brachial reactive hyperemia, and brachial radial pulse wave velocity measured simultaneously	PAT hyperemic response correlated with FMD and brachial hyperemic flow but not pulse wave velocity
Hamburg et al (2008)	1957 adults	PAT and cardiovascular risk factors	PAT hyperemic response lower with male sex, obesity, higher total/HDL cholesterol, diabetes, smoking, lipid-lowering therapy, and higher with increasing age
Referral or disease states			
Kuvin et al (2003)	89 Patients with chest pain referred for stress test	PAT and brachial measured simultaneously	PAT hyperemic response correlated with FMD and lower with risk factors and with positive stress test
Bonetti et al (2004)	94 Patients referred for catheterization	PAT and coronary response to acetylcholine measured	PAT hyperemic response lower in patients with coronary endothelial dysfunction
Haller et al (2007)	44 children	24 with type 1 DM, 20 healthy children	PAT hyperemic response lower in children with DM
Interventional			
Bonetti et al (2003)	23 Patients with refractory angina	7-wk Treatment Enhanced external counterpulsation	PAT hyperemic response increased after treatment
Nohria et al (2006)	19 healthy subjects	Administration of inhibitor of eNOS inhibitor, L-NAME	PAT hyperemic response lower after L-NAME consistent with nitric oxide dependence
Schroeter et al (2006)	12 healthy subjects	Ingestion of flavanol-rich cocoa or epicatechin	Flavanoid consumption increased PAT hyperemic response
Aversa et al (2008)	20 men with diabetes	4-wk Treatment with sildenafil or placebo	Sildenafil increased PAT hyperemic response and FMD

FMD, flow-mediated dilation; DM, diabetes mellitus; eNOS, endothelial nitric oxide synthase; L-NAME, L-nitro-arginine methyl ester.

digital vascular responses in small studies. Polycystic ovarian syndrome, preeclampsia, obstructive sleep apnea, acute malaria infection, depression, mental stress, and postprandial hyperglycemia have all been associated with decreased PAT hyperemic response (Crandall et al. 2009, Itzhaki et al. 2005, Lowenstein et al. 2007, Martin et al. 2008, Tomfohr et al. 2008, Yeo et al. 2007, Yinon et al. 2006). These studies provide evidence that systemic states associated with cardiovascular risk impair microvessel vasodilator function in the fingertip reflected in lower PAT hyperemic responses.

We examined how cardiovascular risk factors relate to PAT measures in the Framingham Heart Study Third Generation cohort. In this large, community-based cohort, we reported that cardiovascular risk factors explained close to 16% of the variability in the PAT hyperemic response (Hamburg et al. 2008). Several cardiovascular risk factors, including male sex, body mass index, total to HDL cholesterol ratio, diabetes mellitus, smoking, and lipid-lowering treatment were all associated with lower PAT hyperemic response. Surprisingly, increasing age was associated with higher PAT hyperemic response. The unanticipated positive association between advancing age and PAT requires further investigation in cohorts with a wider age range and potentially reflects differential aging responses in the digital vessels. Systolic blood pressure and C-reactive protein were not associated with PAT hyperemic response in multivariable models.

We also reported significant relations between cardiovascular risk factors and higher baseline pulse amplitude. Baseline pulse amplitude reflects blood flow, tone, and compliance and may be an important indicator of microvessel structure and function. Overall, these findings suggest that early vascular abnormalities associated with systemic cardiovascular risk factors are reflected in digital vascular responses.

The presence of clinical cardiovascular disease is associated with impaired digital vascular function. Individuals with a stress test with evidence of ischemia had lower PAT hyperemic responses than those individuals without ischemia (Kuvin et al. 2003). In an ambulatory setting, patients with coronary artery disease had lower PAT hyperemic responses than individuals without established coronary disease (Kuvin et al. 2007).

Although cross-sectional studies including large numbers of participants have excellent ability to adjust for potential confounding, they cannot establish the temporal relations between risk factors and PAT. Additional evidence for the utility of the PAT hyperemic response is provided by studies showing that short-term interventions of potential beneficial for vascular health improve the PAT hyperemic response. In patients with refractory angina, enhanced external counterpulsation therapy resulted in higher PAT hyperemic responses and a parallel reduction in anginal symptoms (Bonetti et al. 2003). Flavonoid-containing supplements improved the PAT hyperemic response (Barringer et al. 2008, Fisher et al. 2003, Schroeter et al. 2006). Several additional therapies, including L-arginine infusion, sildenafil, air filtration to reduce particulate matter, treatment of malaria, and therapy for

obstructive sleep apnea, all similarly enhanced the PAT hyperemic response (Aversa et al. 2008, Brauner et al. 2008, Itzhaki et al. 2007, Yeo et al. 2007, 2008). Overall, these studies in small groups of selected individuals indicate that the PAT hyperemic response is a dynamic measure of vascular function.

• Limitations of Digital PAT

There are several limitations to digital vascular function testing as a measure of endothelial function. First, few studies have reported the PAT response to a direct vasodilator such as nitroglycerin; thus, the relative importance of endothelium-dependent and independent vasodilation in the PAT hyperemic response has not been defined in patients with risk factors or in disease states. Second, published studies reporting digital vascular responses have primarily included individuals of European descent; thus, it remains uncertain whether PAT hyperemic response varies by ethnicity or race. Third, digital vascular function is highly responsive to sympathetic tone and thus findings from a controlled research environment may not extend to routine practice settings. Finally, there is a cost associated with the probes and each probe can only be used one time.

• Research Directions

Several important questions require further investigation in order to define the clinical relevance and research utility of PAT for cardiovascular disease. The overall association of digital vascular function with cardiovascular risk factors in the Framingham Heart Study was modest at 16% and the contribution of individual risk factors was small. Thus, the determinants of digital vascular function remain incompletely defined. Future studies will define the heritability and relation of genetic variation to digital vascular function. The PAT hyperemic response, as a measure of microvessel function, may not yield equivalent information to measures of conduit artery vasodilation. Further studies in larger samples are required to define the relation between the PAT hyperemic response and alternate measures of endothelial function. More information regarding the variability in the PAT hyperemic response with time of day, ambient temperature, seasons, and menstrual cycle longitudinally and with disease status are necessary. The studies reporting a change in the PAT response with treatment have largely involved novel therapeutic strategies to improve cardiovascular health. Treatments with more established cardiovascular benefits such as statin therapy exist, and it would be interesting to evaluate the effects of these drugs on PAT measures.

Individuals in the Framingham Heart Study and additional cohorts followed over time for the occurrence of cardiovascular events will provide further information regarding the prognostic relevance of the PAT hyperemic response.

Ongoing studies measuring endothelial function using PAT along with alternate methods will aid in determining the relative prognostic value of each vascular function test. Importantly, for any endothelial function test to assist in clinical risk stratification, the results need to provide incremental risk prediction and reclassification of risk over standard risk factors (Vasan 2006, Pencina et al. 2008). Longitudinal studies will evaluate whether certain groups of individuals will derive particular benefit from digital vascular testing, such as those at intermediate risk of cardiovascular events. In addition, it will be important to establish whether improvements in the PAT hyperemic response are associated with lower cardiovascular risk.

• Summary and Conclusions

There is abundant evidence linking endothelial dysfunction to atherosclerosis and to an increased risk of cardiovascular events. Thus, a simple and accurate endothelial function test is an attractive, noninvasive addition to cardiovascular risk stratification tools. There is considerable interest in developing the test of digital vascular function using PAT as a method for evaluating endothelial function. The advantages of this technique include ease of administration and an automated analysis program that facilitate acquisition of reliable data. Recent studies demonstrate a modest relation between cardiovascular risk factors and digital vasodilator responses. Treatments thought to confer cardiovascular benefit are able to reverse endothelial dysfunction in the fingertip. However, much additional work is needed to define the clinical relevance of the PAT hyperemic response. Further studies evaluating the clinical and genetic determinants and the predictive value of digital vascular function are required to establish the role of PAT in clinical and research practice.

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S1050-1738(09)00051-6 **TCM**

Serine Carboxypeptidases in Regulation of Vasoconstriction and Elastogenesis☆

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Lysosomal carboxypeptidases play important roles in catabolism of proteins and peptides and in posttranslational processing of other lysosomal enzymes. The major lysosomal serine carboxypeptidase A (cathepsin A [CathA]), also known as protective protein, activates and stabilizes two other lysosomal enzymes, β-galactosidase and neuraminidase/sialidase 1. Genetic deficiency of CathA (galactosialidosis) causes the lysosomal storage of sialylated glycoconjugates and leads to a multiorgan pathology. The galactosialidosis patients also show arterial hypertension and cardiomyopathy, conditions not predicted from the lysosomal storage of glycoconjugates. This review summarizes the experimental data suggesting that both cardiovascular pathologies associate with persisted vasoconstrictions and impaired formation of the elastic fibers triggered by the deficiency of CathA. We also discuss the homologous serine carboxypeptidases, Scpep1 and vitellogenic-like carboxypeptidase, that are secreted from endothelial cells and could potentially affect the cardiovascular system. (Trends Cardiovasc Med 2009;19:11–17) © *2009, Elsevier Inc.*

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☆ This work was supported in part by the operating grants from Canadian Institutes of Health Research to AVP and AH and by the operating grant from the Heart and Stroke Foundation of Ontario to AH.

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1050-1738/09/$-see front matter