
Medical Policy



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***Current Policy Effective Date: 9/1/19**
(See policy history boxes for previous effective dates)

Title: Endothelial Function Assessment

Description / Background

Coronary artery disease (CAD) occurs when fatty plaque accumulates inside the coronary arteries and obstructs the supply of oxygenated blood to the heart. CAD usually develops gradually over many years, often without symptoms. It is believed that the inner layer of the coronary artery, the endothelium, becomes damaged over time, particularly in individuals with coronary artery disease, type II diabetes mellitus, hypertension, obesity, renal failure, and hypercholesterolemia.

Vascular endothelial cells line the entire circulatory system, from the heart to the smallest capillaries. The primary function of the endothelium is to regulate vascular tone and structure, providing the balance between vasodilation and vasoconstriction. The endothelium also inhibits and stimulates smooth muscle cell proliferation and migration, and it plays a role in thrombogenesis and fibrinolysis. When these functions are disrupted, endothelial dysfunction occurs, causing damage to the arterial wall. Once the endothelium has been injured, the accumulation of fatty deposits may increase the risk of CAD, along with the individual's family history of heart disease. Some individuals develop symptoms, such as chest pain or shortness of breath, whereas others may never experience symptoms of CAD until they suffer a major cardiovascular event, such as a heart attack.

Endothelial function (EF) assessment (testing) has been investigated as a tool to diagnose endothelial dysfunction and CAD risk. Noninvasive techniques for assessing endothelial function have been developed, including brachial artery ultrasound, peripheral artery tonometry, and infrared light transmission photoplethysmography.

Brachial artery flow-mediated dilation (FMD) emerged in the 1990s, and it has been the most widely used noninvasive method to evaluate endothelial function. In this method, the baseline brachial artery diameter and blood velocity are obtained via ultrasonography. Next, blood flow in the artery is occluded for a specified period of time, typically by the use of a standard blood

pressure cuff placed around the arm. When the cuff is released, there is an acute increase in blood flow through the vessels (hyperemia), which triggers a series of physiological responses that result in smooth muscle relaxation and vasodilation. The degree of brachial arterial vasodilation and blood velocity post-vascular occlusion are measured again via ultrasonography. The calculated increase in diameter and velocity from baseline after the cuff is removed reflects endothelium dependent vasodilation and is a barometer of endothelial function. FMD has several limitations that have prevented its incorporation into clinical practice: technical limitations that require extensive sonographer training, expensive equipment, labor-intensive image analysis, and lack of standardization.

Digital peripheral arterial tonometry (PAT) is similar to brachial artery FMD, but instead of assessing a single vessel, PAT measures hyperemia-induced changes in several small vessels in the fingertip by pulse volume amplitude (PVA). Much like brachial artery FMD, PAT utilizes a standard blood pressure cuff placed around the bicep. The other arm without the cuff serves as the control in the test. Special finger sensors containing volume-sensing probes are placed over the index finger of each hand to monitor the function of the blood vessels. The sensors are connected to a recording device. A reading of the fingers' blood flow rate begins and measures peripheral arterial tone. Next, the blood pressure cuff is inflated, temporarily stopping the flow of blood through the non-dominant arm and hand. After approximately five minutes, the blood pressure cuff is deflated, releasing blood flow through the arterial vessels to the fingers. The finger sensors monitor reactive hyperemia, which is the normal blood flow response that occurs when the blood pressure cuff is released and blood returns to the finger tips. The PAT system automatically converts the changes in peripheral arterial tone into a graph, which is used to assess the blood vessels and their hyperemic response before, during, and after the arm cuff was used on the brachial artery. Digital peripheral arterial tonometry (PAT) differs from brachial artery flow-mediated dilation (FMD) in that the hyperemia-induced changes are measured by an automated system, whereas changes elicited by brachial FMD rely on the observation and expertise of a clinician trained in ultrasonography.

Finally, a third noninvasive method involves a desktop device with fingertip infrared light transmission photoplethysmography, which performs digital pulse volume waveform analysis and generates an automated reflection index (RI). The reflection index is a measure of vascular tone of small arteries. Proponents of this method report that endothelial function can be assessed by measuring the change in RI in response to an endothelium-dependent stimulus, such as a vasoactive drug. A digital volume pulse is obtained by measuring the transmission of infra-red light through the finger pulp. The amount of light is proportional to the volume of blood in the vascular beds of the finger. The average pulse from a recording produces a typical pulse waveform, from which the RI results are obtained.

Regulatory Status

The U.S. Food and Drug Administration (FDA) issued a 510(k) approval for the Endo PAT 2000™ device (Itamar Medical, Ltd., Israel) on November 13, 2003. The device uses a reactive hyperemia procedure to measure the peripheral arterial tonometry or tone (PAT). This device is a next generation version of Itamar's PAT 1000Rd™ (representing peripheral artery tonometer) that the FDA cleared on February 21, 2001.

The Endo PAT 2000 device is a non-invasive device, intended for use as a diagnostic aid in the detection of coronary artery Endothelial Dysfunction (positive or negative) using a reactive hyperemia procedure.

According to the FDA, "the Endo PAT 2000 consists of a main control unit, finger probes and tubing and a software package. The Endo PAT 2000 main control unit is connected to two independent, thimble-shaped, finger mountable probes via two air-conducting tubes. A standard computer is connected to the Endo PAT 2000 main control unit for online display and archiving of device recordings and off-line analysis. The outputs of the Endo PAT 2000 probes are pressure fluctuations sensed at its distal compartment induced by the volume changes of the pulsating digital arteries."

Medical Policy Statement

Endothelial function testing using noninvasive techniques is not established. While these services may be safe, their effectiveness in this clinical indication has not been scientifically determined. Therefore, endothelial function testing is experimental/investigational.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

93938

Rationale

Sharma et al (2018) evaluated the relationship between peripheral vascular endothelial function and exercise electrocardiography (Ex-ECG). Twenty-nine asymptomatic women without cardiac risk factors underwent maximal Bruce protocol exercise treadmill testing and peripheral endothelial function assessment using peripheral arterial tonometry (Itamar EndoPAT 2000) to measure reactive hyperemia index (RHI). The relationship between RHI and Ex-ECG ST-segment depression was evaluated using logistic regression and differences in subgroups using two-tailed t-tests. The mean age was 54 ± 7 years, body mass index 25 ± 4 kg/m², and RHI 2.51 ± 0.66 . Three women (10%) had RHI less than 1.68, consistent with abnormal peripheral endothelial function, while 18 women (62%) met criteria for a positive Ex-ECG based on ST-segment depression in contiguous leads. Women with and without ST-segment depression had similar baseline and exercise vital signs, metabolic equivalents

(METS) achieved, and RHI (all $p > 0.05$). RHI did not predict ST-segment depression. Peripheral vascular endothelial dysfunction did not predict Ex-ECG ST-segment depression. The authors concluded that further work is needed to investigate the utility of vascular endothelial testing and Ex-ECG for IHD diagnostic and management purposes in women.

Matsuzawa et al (2015) examined whether peripheral endothelial function can provide additional clinical value to traditional risk factors for cardiovascular diseases in predicting coronary artery disease. The author included 118 stable patients referred for coronary angiography for chest pain evaluation or due to abnormal stress test results. A natural logarithmic value of the RH-PAT index (Ln_RHI) was acquired before cardiac catheterization by an independent operator. They defined significant CAD as luminal stenosis of at least 70% ($\geq 50\%$ at left main) and/or fractional flow reserve of up to 0.80 in one or more major coronary arteries or their major branches. Results showed levels of Ln_RHI were significantly lower in patients with CAD ($n=60$) compared with patients without CAD ($n=58$; 0.69 ± 0.29 vs. 0.88 ± 0.27 , $P < 0.001$). Ln_RHI was significantly associated with CAD independent from traditional risk factors (odds ratio for a 0.1 decrease in $\text{Ln_RHI} = 1.25$, 95% confidence interval: 1.04-1.52, $P = 0.01$). The net reclassification index was improved when Ln_RHI was added to traditional risk factors (0.62, 95% confidence interval: 0.27-0.97, $P = 0.001$). The authors concluded that peripheral endothelial function improved risk stratification when added to traditional risk factors. RH-PAT is potentially useful for identifying patients at high risk for CAD.(17)

In another case series, van den Heuvel et al (2015), examined the applicability of PAT to detect a low risk of CAD in a chest pain clinic. PAT was performed resulting in reactive hyperemia (RHI) and augmentation (Alx) indices in 93 patients. The patients were risk classified according to HeartScore, Diamond and Forrester pretest probability (DF), exercise testing (X-ECG), and computed tomography calcium scoring (CCS) and angiography (CTA). Correlations, risk group differences and prediction of revascularization within 1 year were calculated. Results showed that RHI correlated with HeartScore ($r = 0.21$, $p = 0.05$), Alx with DF ($r = 0.26$, $p = 0.01$). However, both were not significantly different between normal and ischaemic X-ECG groups. In addition RHI and Alx were similar between low risk as compared with intermediate-to-high risk, based on risk algorithms (RHI: 1.98 (0.67) vs. 1.94 (0.78); Alx: 0.0 (21) vs. 5.0 (25); $p = \text{NS}$), or CCS and CTA (RHI: 1.99 (0.58) vs. 1.89 (0.82); Alx: -2.0 (24) vs. 4.0 (25); $p = \text{NS}$). Finally, RHI and Alx failed to predict revascularization (RHI: OR 1.42, CI 0.65-3.1; Alx: OR 1.02, CI 0.89-1.05). The authors concluded that PAT cannot detect a low risk of CAD, possibly because RHI and Alx vs. X-ECG, CCS and CTA represent independent processes.(18)

In 2014, McIlroy et al reported on a prospective cohort study examining whether endothelial dysfunction identified by RH-PAT would be a useful risk-stratification tool for cardiac adverse events in at-risk adults who are undergoing noncardiac surgery. The study found that RH-PAT alone was not a significant predictor of myocardial injury after surgery or 30-day perioperative cardiac morbidity. However, further analysis suggests that patients with endothelial dysfunction as measured by the RH-PAT combined with the clinical Lee index significantly correlated with increased myocardial injury and 30 day perioperative cardiac morbidity.

Woo et al (2014) conducted a prospective cohort study comparing RH-PAT and FMD in patients with stable angina. The differences in these two methods with respect to coronary artery disease severity and complexity were also examined. In this study, endothelial function was assessed before angiography using brachial artery FMD and RH-PAT. Coronary lesions

were assessed with angiography. Extent of CAD was defined as the number of diseased coronary arteries (>70%) and complexity of CAD was assessed by the SYNTAX score algorithm. The study found that RH-PAT was a fair predictor of CAD and was highly correlated with brachial artery FMD. However, neither RH-PAT nor FMD were found to be accurate at prediction of SYNTAX score >22.

In 2014, Yamamoto et al undertook a study to investigate whether digital reactive hyperemia is associated with restenosis after percutaneous coronary intervention in patients with acute coronary syndrome (ACS). The reactive hyperemia index was calculated using RH-PAT at three weeks and eight months after ACS. RHI was defined as the ratio of the digital pulse volume during reactive hyperemia to that observed at baseline. Restenosis was defined as diameter stenosis of $\geq 50\%$ in the in-segment area based on the findings of quantitative coronary angiography. The study found that RH-PAT was statistically correlated with restenosis at 8 months after percutaneous coronary intervention. However, there was no significant association relative to the predictive value of the index to predict restenosis.

In a 2013 publication, Suessenbacher et al evaluated the prognostic value of peripheral endothelial function testing in patients with cardiovascular disease. Peripheral arterial tonometry (PAT) was performed in 96 patients with significant CAD or < 70% stenosis and $\geq$ three cardiovascular risk factors. Patients were followed for cardiovascular events, such as revascularization, acute coronary syndrome, ischemic stroke, and cardiovascular death for 44 ± 14 months. The study cohort was divided according to the median PAT-ratio (1.91). The combined end point occurred in 14 patients with a PAT ratio below the median (1.91) and in 12 patients with a PAT-ratio of ≥ 1.91 ($p=0.65$). In a subgroup of 76 patients, the PAT-ratio was reassessed after six months. No differences in the event rate were found between the patients who exhibited deterioration ($n=50$) and those who exhibited an improvement in the PAT-ratio of >0.1 ($n=26$; 22 vs. 32%, $p = 0.32$). The combined end point occurred earlier in the patients with a PAT-ratio within the 1st tertile than in those with a PAT-ratio within the 2nd/3rd tertile (11.3 ± 11.0 vs. 27.5 ± 18.6 months, $p=0.03$). The authors concluded that “in patients with established CAD or a high cardiovascular risk profile, the PAT-ratio cannot be used to predict the risk of future cardiovascular events. However, a lower PAT-ratio may be associated with the earlier occurrence of cardiovascular events.”

Kontinen et al (2013) sought to determine the association between lowered endothelial function measured by peripheral arterial tonometry (PAT) and cardio-metabolic risk factors. A total of 312 middle-aged municipal workers underwent a physical medical examination and anthropometry measurements. Levels of total cholesterol, HDL cholesterol, triglycerides, fasting glucose, glycated hemoglobin, and high sensitivity C-reactive protein were taken from the blood samples. PAT measured the increase in digital pulse volume amplitude during reactive hyperemia, and the index of endothelial function, F-RHI, was defined as the ratio of post-deflation amplitude to baseline amplitude. The researchers reported that, male sex was associated with lower F-RHI. In sex-adjusted linear regression models, each of the variables, waist circumference, fasting glucose, glycated hemoglobin, triglycerides, body fat percentage, body mass index, current smoking, and impaired fasting glucose or diabetes were separately associated with lower F-RHI, and HDL cholesterol and resting heart rate were associated with higher F-RHI. HDL cholesterol, sex, body mass index, and current smoking were associated with higher F-RHI, and smoking, male sex and body mass index were associated with lower F-RHI. It was concluded that F-RHI is associated with several cardio-metabolic risk factors; low level of HDL cholesterol, male sex, overweight and smoking being the most important

predictors of a lowered endothelial function. A large part of variation in F-RHI remains accounted for by unknown factors.

Matsuzawa et al (2013) hypothesized that adding RHI as an assessment of endothelial function to a coronary complexity morphological assessment and classical risk score would provide substantial cardiovascular event prognostic information in high-risk patients, including stable patients with established CAD. The researchers performed a two-center prospective study of 528 stable patients at high-risk for cardiovascular events from the years 2006–2011. The RHI was measured before coronary angiography and coronary complexity was assessed by SYNTAXsc, an angiographic scoring system used to evaluate coronary atherosclerosis and anatomy complexity. After optimal therapies, including coronary revascularization, there was follow-up with patients until August 2012. Cardiovascular events consisted of cardiovascular death, myocardial infarction, unstable angina, ischemic stroke, coronary revascularization, heart failure-induced hospitalization, aortic disease, and peripheral arterial disease. During 1468 person-years of follow-up, 105 patients developed cardiovascular events. Multivariate Cox proportional hazards analysis identified B-type natriuretic peptide (BNP), SYNTAXsc, and RHI as independent cardiovascular event predictors. When RHI was added to the FRS, BNP, and SYNTAXsc, net reclassification index was significantly improved (27.5%; $P < 0.0001$), with a significant increase in the C-statistic. The authors noted that the study was “limited because it was a 2-center design with a small patient population. Further multicenter studies will be required to confirm our results in a larger patient population.”

Hamburg et al (2008) evaluated Framingham Heart Study participants ($n=1957$) and the relationship between digital pulse amplitude using a fingertip peripheral arterial tonometry (PAT) device and cardiovascular disease risk factors. Initial findings demonstrated that manually induced, reactive hyperemia resulted in a time-dependent increase in fingertip pulse amplitude. The researchers reported that a number of risk factors were inversely related to the hyperemic response (PAT ratio), including being male, body mass index (BMI), total/high density lipoprotein (HDL) cholesterol, diabetes, smoking, and lipid-lowering treatment. Conversely, increasing age was positively correlated with PAT ratio. While results may suggest a link between certain risk factors and lower digital hyperemic response, a causal relationship between these risk factors and digital vascular function could not be established. The clinical utility and predictive value of digital pulse amplitude have yet to be established. The authors acknowledged that “future longitudinal studies are warranted to provide additional information about the clinical utility of measuring vasodilator function in the finger tip as well as the pathways connecting vascular dysfunction, metabolic risk and cardiovascular disease.”

Summary

There is scarce literature on infrared light transmission photoplethysmography for the assessment of endothelial function. The majority of the literature consists of small, non-randomized controlled, case series.

The optimal methodology for investigating endothelial function is still under debate. There is insufficient evidence in the peer-reviewed medical literature to support the clinical utility and effectiveness of endothelial function testing for cardiovascular disease risk. Most of the available studies report some measure of statistical association of either PAT or brachial artery ultrasound with cardiovascular disease. However, these associations are insufficient to directly demonstrate their clinical utility to accurately predict cardiovascular morbidity. Well-designed studies are needed to demonstrate the clinical usefulness of endothelial function tests to effectively predict cardiovascular events.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

The American College of Cardiology Foundation/American Heart Association Task Force guidelines (2010) for assessment of cardiovascular risk in asymptomatic adults did not recommend brachial or peripheral flow-mediated dilation studies for clinical use.

Government Regulations

National:

No National Coverage Determination (NCD) was identified.

Local:

No Local Coverage Determination (LCD) was identified.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 3, 2019, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/14	6/17/14	6/23/14	Joint policy established
9/1/15	6/19/15	7/16/15	Routine maintenance
9/1/16	6/21/16	6/21/16	Routine policy maintenance. Updated rationale and reference section. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		• Routine maintenance • T code deleted by AMA and not replaced • 93998 (NOC) placed on policy • Recommended for retirement

Next Review Date: Policy retired; no longer subject to routine review

**BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ENDOTHELIAL FUNCTION ASSESSMENT**

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Not covered
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.