

Assessing Endothelial Function:
Overview & Scientific Validation of

EndoPAT



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Overview

For more than a decade Endothelial Dysfunction has been recognized by the medical community as the critical junction between risk factors and clinical disease. It is the earliest detectable stage of cardiovascular disease. Furthermore, it is treatable, and unlike the atherosclerotic plaque which it causes, is even reversible.

EndoPAT is the leading medical device for noninvasive endothelial function assessment. It is FDA-cleared (USA regulation), CE-marked (European regulation), SHONIN-cleared (Japanese regulation) and used in preeminent clinical institutions, research centers and Pharmaceutical clinical phase studies in over 40 countries with thousands of tests performed every month. It is incorporated into numerous multi-center and population-based studies such as the Framingham Heart Study. Research using EndoPAT has yielded more than 100 articles in peer-reviewed journals and abstracts. It is becoming widely recognized as the standard method for endothelial function assessment. Some of the features that make EndoPAT appealing are its ease of use, user-independence and immediate, automatically calculated test results. It provides clinicians with a reliable and reproducible index of endothelial function in a 15-minute, office-based test.

EndoPAT has been extensively reviewed in scientific publications ^{1,2,3,4,5}. It is based on noninvasive Peripheral Arterial Tone (PAT) signal technology described below. It measures endothelium-mediated changes in vascular tone using unique bio-sensors placed on the fingertips. These changes in arterial tone are elicited by creating a down-stream hyperemic response induced by a standard 5-minute occlusion of the brachial artery. Measurements from the contra-lateral arm are used to control for concurrent non-endothelial dependent changes in vascular tone. The automatically calculated result is an index of endothelial function.

The Test

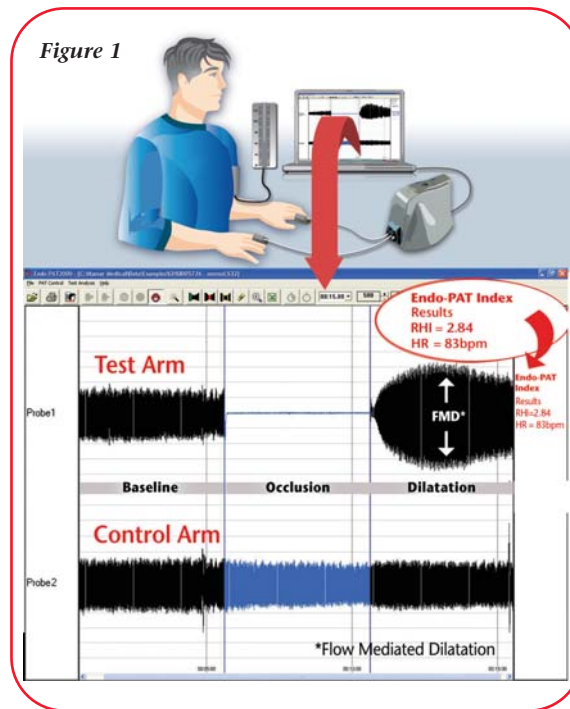
EndoPAT tests can be carried out in both the office and hospital settings, with patients positioned either sitting or supine. EndoPAT bio-sensors are placed on the index fingers of both arms. The test takes 15 minutes to complete, is very easy to perform, and is both operator and interpreter independent. Thermo-neutral, quiet surroundings are recommended.

EndoPAT quantifies the endothelium-mediated changes in vascular tone, elicited by a 5-minute occlusion of the brachial artery (using a standard blood pressure cuff). When the cuff is released, the surge of blood flow causes an endothelium-dependent Flow Mediated Dilatation (FMD). The dilatation, manifested as Reactive Hyperemia, is captured by EndoPAT as an increase in the PAT Signal amplitude. A post-occlusion to pre-occlusion ratio is calculated by the EndoPAT software, providing the EndoPAT index.

Automatic Analysis

EndoPAT software is an integral part of the EndoPAT system. It is straight-forward and easy to use. The software is used for both on-line data acquisition as well as off-line data analysis.

The online display allows real-time viewing of events as they occur. The signals are recorded on the computer for subsequent review and automatic analysis. Since analysis is performed by the software, inter- or intra-operator interpretation variability is avoided. Analyzed test results can be exported to an Excel spreadsheet that includes multiple study parameters, calculated variables, and measures of signal quality.



PAT Technology

Peripheral Arterial Tone (PAT) signal is a proprietary technology used for non-invasively measuring arterial tone changes in peripheral arterial beds⁶. The PAT Signal is measured from the fingertip by recording finger arterial pulsatile volume changes. Based on PAT Technology, the noninvasive EndoPAT system comprises a measurement apparatus that supports a pair of modified plethysmographic bio-sensors. The unique feature of the PAT bio-sensors is that they impart a uniform sub-diastolic pressure field to the distal two thirds of the fingers including their tips. Applying the pressure in this way is extremely important as it:

- Prevents distal venous blood pooling, that can induce a veno-arteriolar vasoconstriction reflex
- Unloads arterial wall tension, which generates a greater dynamic range of the measured PAT Signal
- Fixates the PAT bio-sensor to the finger, which reduces movement artifacts

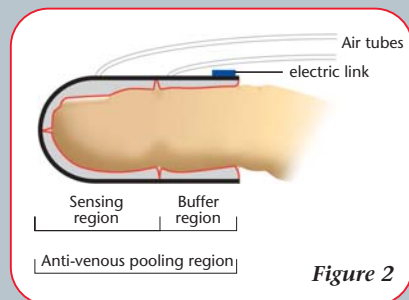


Figure 2



Methodological Advantages

A. Simultaneous recording from both arms:

The subject serves as his/her own control: while endothelial function is tested in one arm, the contra-lateral arm is used to monitor systemic vascular changes (e.g., alterations in autonomic tone, transient environmental effects, etc.) that generally affect both arms. By measuring both arms, EndoPAT corrects for systemic changes that occur during the course of the test.

B. Assessment of occlusion and provocation quality:

The most common way of provoking the endothelium non-invasively is by induction of local ischemia in the arm for 5 minutes. The ischemia is achieved by inflating a blood-pressure cuff to a supra-systolic pressure, causing cessation of blood flow to the arm. In some cases complete occlusion is not achieved, allowing a residual passage of blood that perfuses the downstream tissues. This results in incomplete oxygen starvation necessary to elicit the full endothelial response. EndoPAT enables online detection of occlusion quality allowing the operator to respond by increasing cuff pressure.

C. Large dynamic range of measurement:

The fingers have an inherently large ability to vary local vascular tone, enabling up to a hundred-fold change in blood flow. The pressurized PAT bio-sensors assure greater sensitivity to change, enhancing signal-to-noise ratio and accuracy.

D. Site of measurement:

The fingertips contain small conduit vessels as well as resistance vessels and highly regulated A-V shunts, reflecting a diversity of vascular beds. This further enhances the reliability of EndoPAT.

Advantages



EndoPAT

EndoPAT - Occlusion duration and location

Faizi et al.⁷ tested the effects of varying occlusion durations as well as the effects of occlusion location in 30 apparently healthy adult volunteers.

When comparing different occlusion times (1.5, 3, 5 and 8 minutes) with the cuff placed on the forearm, they saw that the effective maximal response was reached at 5 minutes (Figure 3). The occlusions shorter than 5 minutes had significantly lower responses. The response to a 5 minute occlusion did not differ significantly from 8 minutes, but caused less discomfort.

Twenty individuals of the same study group were tested with the cuff placed on their upper arm, occluding the brachial artery for 5 minutes. These results were compared to their 5 minute forearm occlusion test, showing an EndoPAT index of 1.88 (± 0.55) for the forearm occlusion and 2.07 (± 0.69) for the upper-arm occlusion ($p=0.097$).

Forearm occlusion was reported to cause less discomfort than the upper arm.

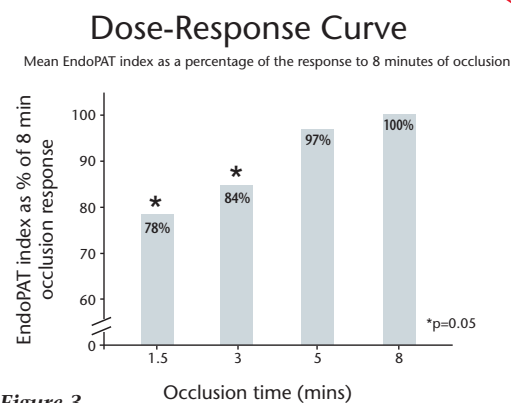


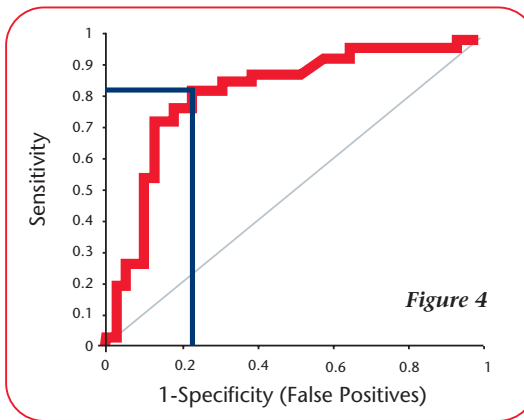
Figure 3

Validation Studies

The essential validity of EndoPAT as a measure of endothelial function has been demonstrated in several independent key studies, at leading medical centers.

A. EndoPAT correlates with assessment of coronary endothelial function

EndoPAT provides high degrees of sensitivity and specificity when compared to the assessment of coronary artery endothelial function. Coronary endothelial function is quantified by measuring arterial diameter change and blood flow in response to graded intra-coronary infusion of Acetylcholine during angiography. In a study performed by Bonetti *et al.* at the Mayo Clinic, Rochester, MN^{8,9}, a group of 94 subjects underwent angiographic assessment of coronary endothelial function and subsequent EndoPAT tests. The results of this comparative study served as the basis for the FDA clearance of the EndoPAT in the detection of coronary endothelial dysfunction. An EndoPAT index cut-off value of 1.67 provides a sensitivity of 82% and a specificity of 77% to diagnosing coronary endothelial function.



B. EndoPAT measures a Nitric-Oxide (NO) mediated response

Nohria and Gerhard *et al.*, at the Brigham & Women's Hospital, Boston, demonstrated the central role for nitric oxide in the post-occlusion vasodilatory response measured by EndoPAT¹⁰. EndoPAT index was measured in a group of nineteen healthy volunteers, before and after intra-arterial infusion of L-NAME (a specific inhibitor of endothelial Nitric Oxide Synthase). Fifteen matched controls were infused with Saline or PhenylEphrine (an endothelium independent vasoconstrictor). The study showed that L-NAME blocked 46% of the vasodilatory response ($p=0.002$). These results provide direct confirmation that EndoPAT indeed measures a NO-mediated endothelial response.

C. Correlation between EndoPAT and Brachial Artery Ultrasound (BAUS)

BAUS is a common research method for peripheral, noninvasive assessment of endothelial function. It differs from EndoPAT in several ways. While the BAUS assesses a single conduit vessel, EndoPAT measures several vascular beds, composed of small vessels and micro-circulation. Furthermore, EndoPAT corrects for systemic changes by a simultaneous measurement from the (un-occluded) contra-lateral arm. With minimal training necessary, EndoPAT is practically operator independent, while BAUS requires a trained ultrasound technician and is highly user-dependent in both data acquisition and analysis. Furthermore, the response measured with EndoPAT has a much larger dynamic range (hundreds of %) than the miniscule changes assessed by BAUS (around 10% for a normal response).

Several studies have simultaneously measured Flow-Mediated Dilatation (FMD) with EndoPAT and BAUS. Kuvin *et al.*¹¹, at the Tufts Medical Center, Boston, demonstrated a significant correlation between the two methods ($r=0.55$, $p<0.0001$) in a group of 89 adult patients suffering from chest pain. In another study by Kuvin *et al.*¹², 60 patients (32 with Coronary Artery Disease (CAD) and 28 without CAD) were studied simultaneously with both EndoPAT and a portable ultrasound. A significant relationship was reported between FMD and the EndoPAT index in both the CAD and non-CAD populations ($r=0.3$; $p<0.05$, for both).

Validation Studies



EndoPAT

A correlation was also reported by Dhindsa *et al.*¹³ who found that the EndoPAT index was significantly and positively associated with BAUS ($r=0.47$, $p<0.01$) in 40 apparently healthy adults. Gurtu *et al.*¹⁴ studied 246 individuals (3 groups: no vascular disease, Inflammatory Bowel Disease and CAD). BAUS and EndoPAT were not correlated; however, EndoPAT index was significantly lower in the CAD group while the BAUS did not differentiate between the patient groups. These results are summarized in table 1.

Table 1: Summary of studies on the relationship between EndoPAT and BAUS

Group (ref)	N	Population	r	p	Comments
Kuvin <i>et al.</i> ¹¹	89	Chest pain	0.55	<0.0001	
Kuvin <i>et al.</i> ¹²	60	CAD(+) and CAD(-)	0.3	<0.05	
Dhindsa <i>et al.</i> ¹³	40	Apparently healthy	0.47	<0.01	
Gurtu <i>et al.</i> ¹⁴	246	Apparently healthy, IBD and CAD(+)	--		Only EndoPAT index is significantly lower in CAD group



D. EndoPAT reproducibility

Several studies demonstrated good reproducibility of EndoPAT. These results are in the upper range or even above the published reproducibility of BAUS assessment of FMD, when operated by a qualified BAUS sonographer. Table 2 provides a summary of the key findings.

Table 2: Summary of EndoPAT reproducibility data

Group	n	Cohort	Time Interval	Statistical Parameter	Result	Comments
Reisner <i>et al.</i> ¹⁵	113	Adult volunteers	24 hours	ICC*	0.56 ($p<0.001$)	Classification of normal vs. dysfunction maintained in 75% of males and 70% of females between days ($p<0.01$)
Selamet Tierney <i>et al.</i> ¹⁶	30	Young adult volunteers	1 to 7 days	ICC*	0.78 ($p<0.001$)	
Tomfohr <i>et al.</i> ¹⁷	12	Young adult volunteers	1 to 7 days	ICC*	0.73 ($p<0.001$)	
JT Kuvin – Tufts Medical Center	47	Adults with chest pain	24 hours	ICC*	0.59 ($P=0.001$)	Part of FDA submission - unpublished data
Haller <i>et al.</i> ¹⁸	44	Type 1 Diabetes adolescents	4 weeks	Coefficient of variation	14.8%	

* ICC - Intra-Class Correlation

E. EndoPAT index as a predictor of Cardiovascular (CV) outcome

Rubinshtein *et al.*¹⁹ assessed the incremental value of the EndoPAT index to the Framingham Risk Score (FRS) in a cohort of 270 outpatients. Major Adverse Cardiovascular Events (MACE) that are cardiac death, myocardial infarction, revascularization or cardiac hospitalization, were recorded over an average follow-up period of 5.8 years. The rate of MACE in patients who tested positive for endothelial dysfunction was 39% vs. normal endothelial function 25% ($p=0.024$). The study showed that patients at low FRS risk but with Endothelial Dysfunction were at a higher actual risk of future CV events than patients with high FRS but normal Endothelial Function (see figure 5). Furthermore, Endothelial Dysfunction was found to be an independent risk factor for future MACE on multivariate analysis ($p=0.002$).

Validation Studies



Outcomes Response Curve EndoPAT vs. Framingham Risk Score

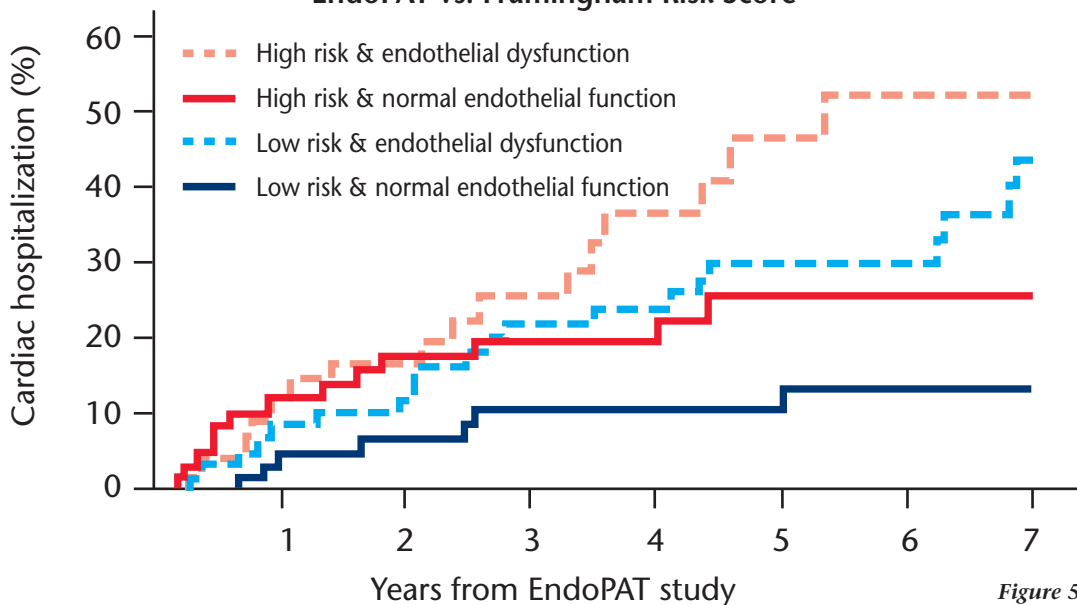


Figure 5

F. Correlation of EndoPAT scores to traditional CV risk factors

Since 2003 the Framingham Heart Study has included endothelial function measurements with EndoPAT. All three study cohorts (the original study population, the Offspring and the 3rd generation cohort) have been tested with EndoPAT, totaling over 5,000 subjects. A cross-sectional analysis of 1,957 3rd Generation subjects was published in *Circulation* (May 2008) by Hamburg *et al.*²⁰ The study demonstrated a significant inverse relation between EndoPAT index and multiple CV risk factors, including: male sex, body mass index, total/HDL cholesterol, diabetes, smoking and lipid-lowering treatment.

A publication from the KORA/Monica cohort²¹ reported a significant inverse correlation of the EndoPAT index with age, BMI, waist circumference, systolic and diastolic blood pressures, Total/HDL Cholesterol ratio, Triglycerides and fasting and 2 hour glucose. HDL Cholesterol was positively correlated to the EndoPAT index.

Bonetti *et al.*⁸ reported significant relationships between EndoPAT index and obesity and HDL levels. Kuvin *et al.* found that EndoPAT index inversely correlated with the number of cardiovascular risk factors¹⁷. In another study by Kuvin *et al.* an inverse correlation was shown between EndoPAT index and the number of cardiovascular risk factors ($r = 0.3$, $P < 0.002$)¹². EndoPAT index was lower in patients with hypertension, hyperlipidemia, tobacco use, and a family history of CAD.

G. EndoPAT: separation of clinically distinct populations in case - control studies

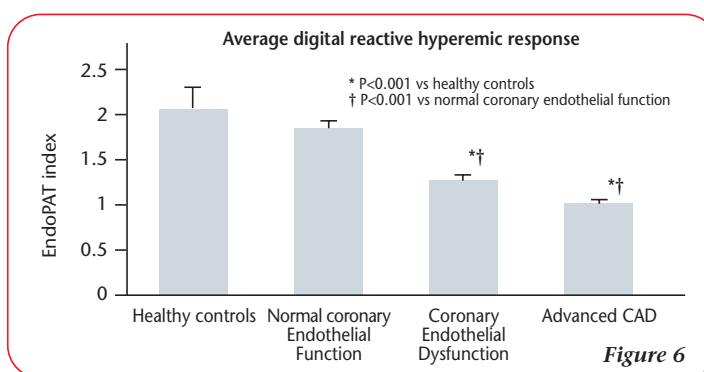
The discriminative ability of EndoPAT between degrees of known CVD risk has been evaluated according to the number of cardiovascular risk factors, the results of myocardial perfusion imaging, or by assessing CAD patients vs. apparently healthy controls.

Bonetti²² assessed 118 subjects, divided into 4 groups:

1. 12 healthy volunteers
2. 39 patients with chest pain and normal coronary endothelial function
3. 55 patients with chest pain and coronary endothelial dysfunction
4. 12 patients with advanced CAD

This study demonstrated that EndoPAT index is similarly and significantly attenuated in patients with early and advanced CAD (groups 3 and 4 above) compared with healthy individuals or subjects with a healthy coronary endothelium (groups 1 and 2 above; see figure 6). A significant separation between CAD patients and controls was also shown by Kuvin *et al.*¹² who observed a significantly lower EndoPAT index in CAD(+) subjects compared to CAD(-) ($p < 0.05$).

In another study by Kuvin *et al.*¹¹ the EndoPAT index was assessed in 68 patients with chest pain, who performed exercise Myocardial Perfusion Imaging (SPECT Sestamibi). The index was significantly lower in those with positive exercise myocardial perfusion, indicative of ischemic heart disease.



Robertsson *et al.*²³ studied 133 patients referred for myocardial perfusion imaging (MPI). EndoPAT index was significantly lower in the group with perfusion defects than in the group without perfusion defects ($p = 0.003$). Furthermore, EndoPAT index was significantly lower in the group with reversible perfusion defects than in the group without reversible defects ($p = 0.01$). In a multivariate analysis model, adjusting for age, gender, BMI and diastolic blood pressure, the EndoPAT index was the only independent predictor of reversible perfusion defects ($p < 0.05$).

Endothelial dysfunction is believed to be a pan-systemic disease associated with numerous disease states. The EndoPAT index was shown to separate cases from controls in various disease populations including: Type 1 and 2 diabetes^{18,24,25,26} and glucose intolerance^{27,28}, Poly Cystic Ovary Syndrome²⁹, Pre-Eclamptic Toxemia³⁰, Inflammatory Bowel Disease^{31,32}, Systemic Lupus Erythematosus³³, mood disorders^{17,34}, Pulmonary HTN³⁵ and Obstructive Sleep Apnea³⁶.

H. EndoPAT: response to treatment

Endothelial Dysfunction has been shown to respond well to treatment. Broadly, treatment options fall into 3 main categories:

1. Lifestyle modification (including dietary changes, exercise etc)
2. Drugs - through pleiotropic effects, (e.g. Statins), or directly, (e.g., Tetra-Hydro Biopterin, L-Arginine)
3. Treatment of co-morbidities (e.g., glycemic control for diabetics)

Several EndoPAT studies have demonstrated improvement in endothelial function as a result of a variety of clinical interventions. These are collated in Table 3.



Table 3: EndoPAT studies demonstrating improvement in endothelial function

Category	Intervention	Reference
Lifestyle modification	Smoking cessation	Komatsu <i>et al.</i> ³⁷
Dietary changes	Flavonoids	Schroeter <i>et al.</i> ³⁸ , Fisher <i>et al.</i> ³⁹ , Barringer <i>et al.</i> ⁴⁰ , Fisher <i>et al.</i> ⁴¹ , Hollenberg <i>et al.</i> ⁴²
	Omega 3	Dangardt <i>et al.</i> ⁴³
	Low carb/fat diet	Davis <i>et al.</i> ⁴⁴
	Conjugated Linoleic Acid	Fielitz <i>et al.</i> ⁴⁵
Devices for co-morbidity	EECP	Bonetti <i>et al.</i> ⁴⁶
	Oral Appliances	Ithzhaki <i>et al.</i> ⁴⁷ Pillar ⁴⁸
	CPAP	Ithzhaki <i>et al.</i> ⁴⁹ , Morgenthaler <i>et al.</i> ⁵⁰
Drugs	PDE5-I	Prince <i>et al.</i> ⁵² Aversa <i>et al.</i> ⁵³
	BH4	Hsu <i>et al.</i> ⁵¹
	L-Arginine	Yeo <i>et al.</i> ^{54,55}
	Eplerenone	Thum <i>et al.</i> ⁵⁶
	Clopidogrel	Luu <i>et al.</i> ⁵⁷

Cutting-edge Research

In addition to the aforementioned studies, EndoPAT has been employed in numerous clinical studies. Some prominent large studies which use EndoPAT are:

Table 4: Large clinical studies using EndoPAT

Study Name & Academic Institution	Cohort Size	Goal
Framingham Heart Study* (Original Cohort, Offspring, Generation 3) Boston University, MA	Subset of 5,000 tested by EndoPAT	Improve CV risk stratification
Gutenberg Heart Study (formerly PREVENT-IT)* Johannes Gutenberg University Mainz, Germany	17,000	Develop new CV risk score based on subclinical disease, proteomics and genomics
Emory Health Gene Bank Emory University Atlanta, GA	Subset of 5,000 tested by EndoPAT	Establish a clinical & genetic database of cardiac patients
META-Health Emory & Morehouse Universities Atlanta, GA	1,000 individuals aged 30-65	Ethnic differences in obesity-related CVD and new intervention strategies
Heart SCORE (Heart Strategies Concentrating On Risk Evaluation) University of Pittsburgh Medical Center, PA	700 Caucasians & 700 African-Americans	The role of Endothelial Dysfunction in racial disparities of CVD
Jackson Heart Study* Jackson State Uni., Tougaloo College, Uni. of MS Medical Center, Jackson, MS	Subset of 3,000 tested by EndoPAT	CVD risk in African Americans: etiology & treatment strategies
KORA* - Cooperative Health Research Johannes Gutenberg-University Augsburg, Germany	Subset of 1,000 tested by EndoPAT	Regional research platform for population-based surveys of CVD risk factors & their pathophysiology

* Population-based longitudinal study



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EndoPAT

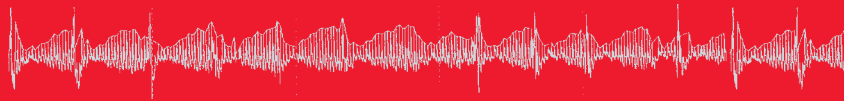
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