

Assessing Endothelial Function:  
Overview & Scientific Validation of

# Endo-PAT2000



**itammar**

Itamar Medical



## 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.

Endo-PAT2000 is the leading medical device for noninvasive endothelial function assessment. It is FDA-cleared, CE-marked and used in preeminent clinical institutions, research centers and Pharmaceutical clinical phase studies in over 40 countries. It is incorporated into numerous multi-center and population-based studies such as the Framingham Heart Study. Research using Endo-PAT 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 Endo-PAT 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.

Endo-PAT 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

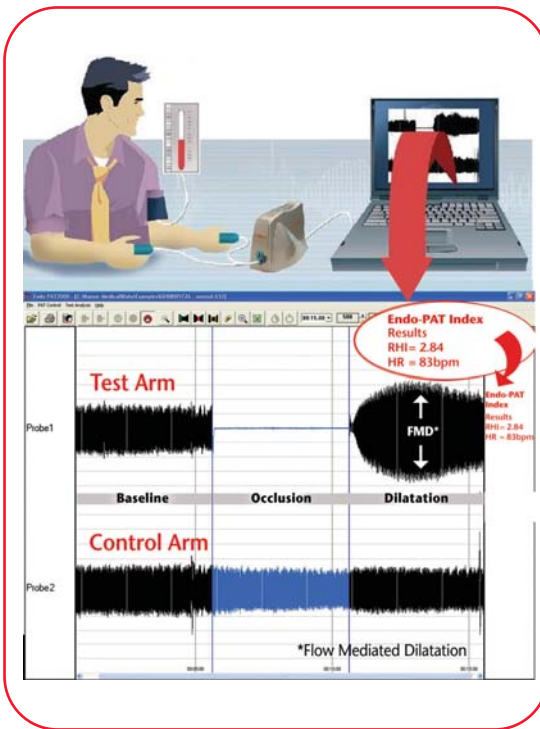
Endo-PAT tests can be carried out in both the office and hospital settings, with patients positioned either sitting or supine. Endo-PAT bio-sensors are placed on the index fingers of both arms. The test takes 15 minutes to complete, is very easy to perform, and is both operator and interpreter independent.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

Endo-PAT 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 Endo-PAT as an increase in the PAT Signal amplitude. A post-occlusion to pre-occlusion ratio is calculated by the Endo-PAT software, providing the EndoScore.

## Automatic Analysis

Endo-PAT software is an integral part of the Endo-PAT 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.

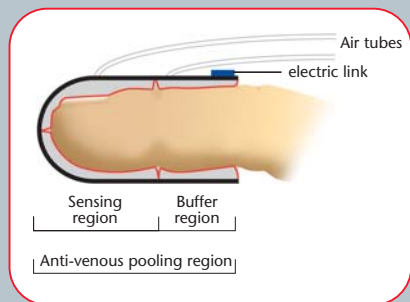
The online display allows real-time viewing of events as they occur. The signals are recorded on the computer for subsequent review and automatic analysis. Since analysis is performed by the software, inter- or intra-operator interpretation variability is avoided. Analyzed test results can be exported 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 beds<sup>1</sup>. The PAT Signal is measured from the fingertip by recording finger arterial pulsatile volume changes. Based on PAT Technology, the noninvasive Endo-PAT2000 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



# 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, Endo-PAT2000 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. Endo-PAT2000 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 Endo-PAT.

## Advantages



Endo-PAT2000

# Validation Studies

The essential validity of Endo-PAT2000 as a measure of endothelial function has been demonstrated in several independent key studies, at leading medical centers.

## A. Endo-PAT correlates with assessment of coronary endothelial function

Endo-PAT 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<sup>2,3</sup>, a group of 94 subjects underwent angiographic assessment of coronary endothelial function and subsequent Endo-PAT tests. The results of this comparative study served as the basis for the FDA clearance of the Endo-PAT in the detection of coronary endothelial dysfunction. An EndoScore cut-off value of 1.67 provides a sensitivity of 82% and a specificity of 77% to diagnosing coronary endothelial function.

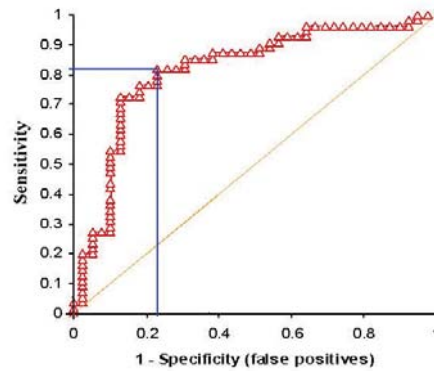


Figure 1

## B. Endo-PAT 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 Endo-PAT<sup>4</sup>. The EndoScore 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 Endo-PAT indeed measures a NO-mediated endothelial response.

## C. Correlation between Endo-PAT and Brachial Artery Ultrasound (BAUS)

BAUS is a common research method for peripheral, noninvasive assessment of endothelial function. It differs from Endo-PAT in several ways. While the BAUS assesses a single conduit vessel, Endo-PAT measures several vascular beds, composed of small vessels and micro-circulation. Furthermore, Endo-PAT corrects for systemic changes by a simultaneous measurement from the (un-occluded) contra-lateral arm. With minimal training necessary, Endo-PAT 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 Endo-PAT 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 Endo-PAT and BAUS. Kuvin *et al.*<sup>5</sup> 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.*<sup>6</sup>, 60 patients (32 with Coronary Artery Disease (CAD) and 28 without CAD) were studied simultaneously with both Endo-PAT and a portable ultrasound. A significant relationship was reported between FMD and the EndoScore in both the CAD and non-CAD populations ( $r=0.3$ ;  $p<0.05$ , for both).

## Validation Studies



Endo-PAT2000

A correlation was also reported by Dhindsa *et al.*<sup>7</sup> who found that the EndoScore was significantly and positively associated with BAUS ( $r=0.47$ ,  $p<0.01$ ) in 40 apparently healthy adults. Gurtu *et al.*<sup>8</sup> studied 246 individuals (3 groups: no vascular disease, Inflammatory Bowel Disease and CAD). BAUS and Endo-PAT were not correlated; however, Endo-PAT 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 Endo-PAT and BAUS**

Group (ref)	N	Population	r	p	Comments
Kuvin <i>et al.</i> <sup>5</sup>	89	Chest pain	0.55	<0.0001	
Kuvin <i>et al.</i> <sup>6</sup>	60	CAD(+) and CAD(-)	0.3	<0.05	
Dhindsa <i>et al.</i> <sup>7</sup>	40	Apparently healthy	0.47	<0.01	
Gurtu <i>et al.</i> <sup>8</sup>	246	Apparently healthy, IBD and CAD(+)	--		Only EndoScore is significantly lower in CAD group
Erbs <i>et al.</i> <sup>9</sup>	15	Obese adolescents	0.9		

### D. Endo-PAT reproducibility

Several studies demonstrated good reproducibility of Endo-PAT. 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 Endo-PAT reproducibility data**

Group	n	Cohort	Time interval	Statistical Parameter	Result	Comments
Reisner <i>et al.</i> <sup>10</sup>	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> <sup>11</sup>	30	Young adult volunteers	1 to 7 days	ICC*	0.78 ( $p<0.001$ )	
Tomfohr <i>et al.</i> <sup>12</sup>	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> <sup>13</sup>	44	Type 1 Diabetes adolescents	4 weeks	Coefficient of variation	14.8%	

\* ICC - Intra-Class Correlation

### E. EndoScore as a predictor of Cardiovascular (CV) outcome

Rubinshtein *et al.*<sup>14</sup> assessed the incremental value of the EndoScore to the Framingham Risk Score (FRS) in a cohort of 270 outpatients. Major Adverse Cardiovascular Events (MACE) that





## Outcomes Response Curve Endo-PAT vs. Framingham Risk Score

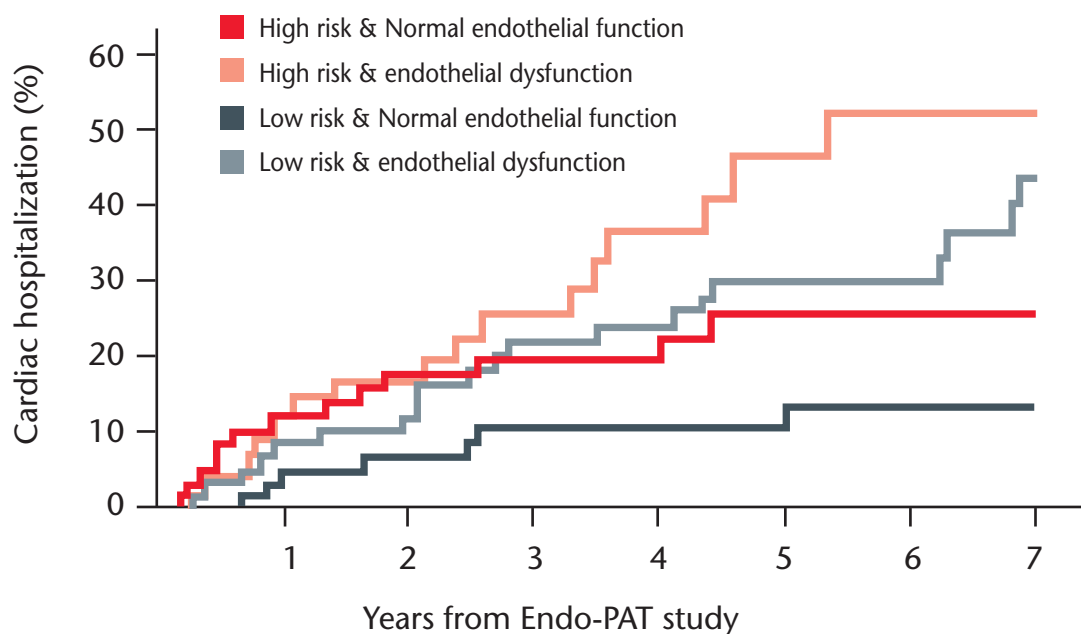


Figure 2

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. Furthermore, Endothelial Dysfunction was found to be an independent risk factor for future MACE on multivariate analysis ( $p=0.002$ ) (see figure 2).

### F. Correlation of EndoScore to traditional CV risk factors

Since 2003 the Framingham Heart Study has included endothelial function measurements with Endo-PAT. All three study cohorts (the original study population, the Offspring and the 3rd generation cohort) have been tested with Endo-PAT, 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.*<sup>15</sup>. The study demonstrated a significant inverse relation between EndoScore 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 cohort<sup>16</sup> reported a significant inverse correlation of the EndoScore 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 EndoScore.

Bonetti *et al.*<sup>2</sup>. reported significant relationships between EndoScore index and obesity and HDL levels. Kuvin *et al.* found that EndoScore inversely correlated with the number of cardiovascular risk factors<sup>5</sup>. In another study by Kuvin *et al.* an inverse correlation was shown between EndoScore and the number of cardiovascular risk factors ( $r = 0.3$ ,  $P < 0.002$ )<sup>6</sup>. EndoScore was lower in patients with hypertension, hyperlipidemia, tobacco use, and a family history of CAD.

## G. Endo-PAT: separation of clinically distinct populations in case/control studies

The discriminative ability of Endo-PAT 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.

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 EndoScore 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 3). A significant separation between CAD patients and controls was also shown by Kuvin *et al.*<sup>6</sup> who observed a significantly lower EndoScore in CAD(+) subjects compared to CAD(-) ( $p < 0.05$ ).

In another study by Kuvin *et al.*<sup>5</sup> the EndoScore 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.*<sup>18</sup> studied 133 patients referred for myocardial perfusion imaging (MPI). EndoScore was significantly lower in the group with perfusion defects than in the group without perfusion defects ( $p = 0.003$ ). Furthermore, EndoScore 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 EndoScore was the only independent predictor of reversible perfusion defects ( $p < 0.05$ ).

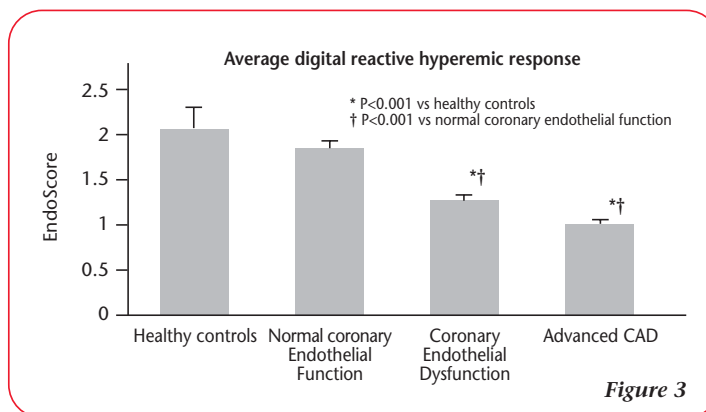
Endothelial dysfunction is believed to be a pan-systemic disease associated with numerous disease states. The EndoScore was shown to separate cases from controls in various disease populations including: Type 1 and 2 diabetes<sup>13,19,20,21</sup> and glucose intolerance<sup>22,23</sup>, Poly Cystic Ovary Syndrome<sup>24</sup>, Pre-Eclamptic Toxemia<sup>25</sup>, Inflammatory Bowel Disease<sup>26,27</sup>, Systemic Lupus Erythematosus<sup>28</sup>, mood disorders<sup>12, 29</sup>, Pulmonary HTN<sup>30</sup> and Obstructive Sleep Apnea<sup>31</sup>.

## H. Endo-PAT: 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 Endo-PAT studies have demonstrated improvement in endothelial function as a result of a variety of clinical interventions. These are collated in Table 3.



## Validation Studies



Endo-PAT2000

**Table 3: Endo-PAT studies demonstrating improvement in endothelial function**

Category	Intervention	Reference
Lifestyle modification	Smoking cessation	Komatsu <i>et al.</i> <sup>32</sup>
Dietary changes	Flavonoids	Schroeter <i>et al.</i> <sup>33</sup> , Fisher <i>et al.</i> <sup>34</sup> , Barringer <i>et al.</i> <sup>35</sup> , Fisher <i>et al.</i> <sup>36</sup> , Hollenberg <i>et al.</i> <sup>37</sup>
	Omega 3	Dangardt <i>et al.</i> <sup>38</sup>
	Low carb/fat diet	Davis <i>et al.</i> <sup>39</sup>
	Conjugated Linoleic Acid	Fielitz <i>et al.</i> <sup>40</sup>
Devices for co-morbidity	EECP	Bonetti <i>et al.</i> <sup>41</sup>
	Oral Appliances	Ithzhaki <i>et al.</i> <sup>42</sup> Pillar <sup>43</sup>
	CPAP	Ithzhaki <i>et al.</i> <sup>44</sup> , Morgenthaler <i>et al.</i> <sup>45</sup>
Drugs	PDE5-I	Prince <i>et al.</i> <sup>47</sup> Aversa <i>et al.</i> <sup>48</sup>
	BH4	Hsu <i>et al.</i> <sup>46</sup>
	L-Arginine	Yeo <i>et al.</i> <sup>49,50</sup>
	Eplerenone	Thum <i>et al.</i> <sup>51</sup>
	Clopidogrel	Luu <i>et al.</i> <sup>52</sup>

## Cutting-edge Research

In addition to the aforementioned studies, Endo-PAT has been employed in numerous clinical and basic science protocols (several in press or in preparation). The inherent ease of use, short learning curve, scientific validation, standardization and objectivity make Endo-PAT2000 an excellent method for both the office-based clinical setting and for large-scale diagnostics. Some prominent large scale studies which use Endo-PAT are:

- **Gutenberg Heart Study (formerly PREVENT-IT)** – Johannes Gutenberg University, in Mainz, Germany, is a highly advanced epidemiological study of cardiovascular risk factors in a non selected adult population of over 17,000 participants. The aim of the study is the development of a score for cardiovascular risk stratification, taking into account subclinical disease, protein patterns and genetic variability.
- **Gene Bank at Emory University**, Atlanta, GA, aims to establish a large database of cardiac catheterization and heart failure patients from the Emory Health System. Each individual undergoes advanced clinical tests and genetic analysis. From this cohort, 5,000 patients will be tested with Endo-PAT.
- **META-Health at Emory & Morehouse Universities**, Atlanta, GA. The goal of the study is to assess ethnic differences between African-Americans and whites in obesity-related cardiovascular disease and discovering new intervention strategies. The aim is to recruit a cohort of 1,000 individuals between the ages 30-65 years.
- **University of Pittsburgh Medical Center (UPMC)** – “The Role of Arterial Endothelial Dysfunction in Racial Disparities of Cardiovascular Disease”, part of Heart SCORE (**Heart Strategies Concentrating On Risk Evaluation**) study. A community based, outcome study, with a cohort of 2,000 subjects, half Caucasians and half African-Americans.
- **Jackson Heart Study** is a large scale, epidemiological study located in the Delta of the Mississippi where cardiovascular mortality is the highest in the US. Endo-PAT has been incorporated in the study since 2007.
- **KORA - Cooperative Health Research, Augsburg, Germany**, formerly WHO MONICA study, is a regional research platform for population-based surveys and subsequent follow-up studies. Endo-PAT is used in a subset of over 1,000 patients.



## References

1. Schnall RP, Shlitner A, Sheffy J, Kedar R, Lavie P. **Periodic, Profound Peripheral Vasoconstriction – A New Marker of obstructive Sleep Apnea.** *SLEEP* 1999; 22(7):939-46
2. Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr., Kuvin JT, Lerman A. **Noninvasive Identification of Patients with Early Coronary Atherosclerosis by Assessment of Digital Reactive Hyperemia.** *JACC* 2004; 44: 2137-2141
3. Bonetti PO et al. Research Highlights – editorial review of **A Noninvasive Test for Endothelial Dysfunction.** *Nature Clinical Practice Cardiovascular Medicine* 2005; 2: 64-65
4. Nohria A, Gerhard-Herman M, Creager MA, Hurley S, Mitra D, Ganz P. **The Role of Nitric Oxide in the Regulation of Digital Pulse Volume Amplitude in Humans.** *J Appl Physiol* 2006; 101:545-8
5. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH, Udelson JE. **Assessment of Peripheral Vascular Endothelial Function with Finger Arterial Pulse Wave Amplitude.** *AHJ* 2003; 146: 168-74
6. Kuvin JT, Mammen A, Mooney P, Alsheikh-Ali A, Karas RH. **Assessment of Peripheral Vascular Endothelial Function in the Ambulatory Setting.** *Vascular Medicine* 2007; 12:13-16
7. Dhindsaa M, Sommerlada SM, DeVana AE, Barnes JN, Sugawara J, Leyb O, Tanaka H. **Inter-relationships Among Noninvasive Measures of Postischemic Macro- and Micro-Vascular Reactivity.** *Journal of Applied Physiology* 2008; 105:398-9
8. Gurtu V, Chan S, Sun Y, Philpott A, Anderson TJ. **Peripheral Arterial Tonometry (Pat-Index) As A Determinant Of Vascular Function And Cardiovascular Health.** Canadian Cardiovascular Congress Oct 2008
9. Erbs et al. **Vascular Dysfunction in Obese Children.** *ESC* 2008
10. Reisner Y, Lusky R, Shay-El Y, Schnall R, Herscovici S. **Reproducibility of endothelial function and arterial stiffness assessed using finger peripheral arterial tonometry.** *EHJ* 2007; 28 (Suppl.):484
11. Selamet Tierney ES, Newburger JW, Gauvreau K, Geva J, Coogan E, Colan SD, Ferranti SD. **Endothelial Pulse Amplitude Testing: Feasibility and Reproducibility in Adolescents.** *J Pediatr.* 2009 Feb 12. [Epub ahead of print]
12. Tomfohr LM, Martin TM, Miller GE. **Symptoms of depression and impaired endothelial function in healthy adolescent women.** *J Behav Med* 2008; 31:137-143
13. Haller MJ, Stein J, Shuster J, Theriaque D, Silverstein J, Schatz DA, Earing MG, Lerman A, Mahmud FH. **Peripheral Artery Tonometry Demonstrates Altered Endothelial Function in Children With Type 1 Diabetes.** *Pediatric Diabetes* 2007; 8:193-198
14. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Nelson RE, Pumper GM, Lerman LO, Lerman A. **A Assessment of Endothelial Function by Peripheral Arterial Tonometry Predicts Cardiovascular Events Beyond the Framingham Risk Score.** *JACC* 2009; Suppl.
15. Hamburg NM, Keyes MJ, Larson MG, Vasan RS, Schnabel R, Pryde MM, Mitchell GF, Sheffy J, Vita JA, Benjamin EJ **Cross-Sectional Relations of Digital Vascular Function to Cardiovascular Risk Factors in the Framingham Heart Study.** *Circulation* 2008; 117: 2467-2474
16. B. Thorand, A. Schneider, A. Peters, W. Rathmann, H.-E. Wichmann, C. Meisinger. **Association of endothelial function with components of the metabolic syndrome and lifestyle factors in subjects without previously diagnosed diabetes: Results from the KORA F4 Study (2006-2008).** *EASD Sep 2008*
17. Bonetti PO. **Attenuation of Digital Reactive Hyperemia in Patients with Early and Advanced Coronary Artery Disease.** *JACC* 2005; 45(3) (Suppl):407A.
18. Per Robertsson P, Ulrika Hagg, Ann wittfeldt, Milan Lomsky, Li-ming Gan. **Determinates and Prognostic value of Peripheral Arterial Tone in healthy volunteers and patients with suspected Coronary Artery Disease.** *Arteriosclerosis, Thrombosis and Vascular Biology Annual Conference 2008*
19. Mahmud FH, Earing MG, Lee RA, Lteif AN, Driscoll DJ, Lerman A. **Altered Endothelial Function in Asymptomatic Male Adolescents with Type 1 Diabetes.** *Congenital Heart Disease* 2006; 1:98-103
20. Mahmud FH, Van Uum S, Kanji N, Thiessen-Philbrook H, Clarson CL. **Impaired endothelial function in adolescents with type 1 diabetes mellitus.** *J Pediatr.* 2008; 152(4):557-62
21. Shachor-Meyouhas Y, Pillar G, Shehadeh N. **Uncontrolled Type 1 Diabetes Mellitus and Endothelial Dysfunction in Adolescents.** *IMAJ* 2007; 9:637-640
22. Crandall J, Shamooh H, Gajavelli S, Reid M, Cohen H, Barzilai N. **Impaired Endothelial Function in Elderly Subjects with Isolated Post-Challenge Hyperglycemia.** *ADA* 2006
23. Lang CC, ALZadjali MA, Godfrey V, Choy A, Khan F, Struthers A.D. **Prevalence of Insulin Resistance Among Non-Diabetic Chronic Heart Failure Patients And Its Relation To Disease Severity.** *Circulation* 2007; 116: II\_705-II\_706
24. Lowenstein L, Damti A, Pillar G, Shott S, Blumenfeld Z. **Evaluation of Endothelial Function in women with Polycystic Ovary Syndrome.** *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2007;134:208-12
25. Yinon D, Levenstein L, Suraya S, Beloosesky R, Zmora O, Malhotra A, Pillar G. **Pre-eclamptic toxemia is associated with sleep disordered breathing and endothelial dysfunction.** *European Respiratory Journal* 2006; 27:328-33
26. Roifman I, Fedwick JP, Sun YC, Panaccione R, Beck PL, Rostom A, Anderson TJ. **Evidence of microvascular endothelial dysfunction in inflammatory bowel disease patients.** *Can J Cardiol* 2007;23:159C
27. Roifman I, Fedwick JP, Panaccione R, Lui H, Anderson TJ, Beck PL. **Patients with Inflammatory Bowel Disease Have Evidence of Systemic Endothelial Dysfunction.** *Gastroenterol* 2007;132(4) (Suppl. 2):A-65
28. Lee PY, Li Y, Richards HB, Chan FS, Zhuang H, Narain S, Butfiloski EJ, Sobel ES, Reeves WH, Segal MS **Type I interferon as a novel risk factor for endothelial progenitor cell depletion and endothelial dysfunction in systemic lupus Erythematosus.** *Arthritis & Rheumatism*; 56: 3759-3769
29. Osika W, Montgomery S, Dangardt F, Währborg P, Volkmann R, Gan L, Eva T, Friberg P. **Anger, Depression And Anxiety Are Associated With Endothelial Function In Childhood.** *Circulation* 2007;116:II-633

## References



Endo-PAT2000

30. Peled N, Bendayan D, Shitrit D, Fox B, Yehoshua L, Kramer MR. **Peripheral Endothelial Dysfunction in Patients with Pulmonary Arterial Hypertension.** *Respiratory Medicine* 2008; 102: 1791-1796
31. Itzhaki S et al. **Endothelial Dysfunction in Obstructive Sleep Apnea Measured by Peripheral Arterial Tone Response in the Finger to Reactive Hyperemia.** *SLEEP* 2005; 28:594-600
32. Komatsu H, Hara H, Nemoto N, Itou S, Takagi T, Nakamura M, Sugli K. **Only short-term smoking cessation improves endothelial dysfunction; non-invasive evaluation used new device, Endo-PAT 2000.** *EHI* 2007; 28 (Suppl.):587
33. Schroeter H, Hiess C, Balzer J, Kleinbongard P, Keen C, Hollenberg N, Sies H, Kwik-Urbe C, Schmitz H, Kelm M. (-)-Epicatechin Mediates Beneficial Effects of Flavanol-Rich Cocoa on Vascular Function in Humans. *PNAS* 2006; 103:1024-1029
34. Fisher N, Hughes M, Gerhard-Herman M, Hollenberg NK. **Flavanol-Rich Cocoa Induces Nitric-Oxide-Dependent Vasodilation in Healthy Humans.** *Journal of Hypertension* 2003; 21:2281-2286
35. Barringer TA, Hatcher L, Sasser HC. **Potential Benefits on Impairment of Endothelial Function after a High-fat Meal of 4 weeks of Flavonoid Supplementation.** *Evid Based Complement Alternat Med* 2007; 14:1-6 (ePub)
36. Fisher ND, Hollenberg NK. **Aging and vascular responses to flavanol-rich cocoa.** *Journal of Hypertension* 2006; 24:1575-1580
37. Hollenberg NK, Fisher ND. **Is It the Dark in Dark Chocolate.** *Circulation* 2007; 116: 2360-2362
38. Dangardt F, Osika W, Chen Y, Gronowitz E, Strandvik B, Friberg P. **Supplement with Omega 3 Fatty Acids Lowers Pulse Wave Velocity in Obese Adolescents.** *Circulation* 2007; 116: 11-827
39. Davis N, Katz S, Wylie-Rosett J, Crandall J **Effects of Low-Carbohydrate and 14 Low-Fat Diets on Inflammation and Endothelial Function.** *AHA Nutrition, Physical Activity and Metabolism Conference* 2008
40. Fielitz K, Helwig U, Rubin D, Pfeuffer M, Winkler P, Laue C, Schwedhelm E, Boger RH, Bell D, Schrezenmeier J. **The effect of CLA on endothelial function & traits of the metabolic syndrome.** *EASD* 2007
41. Bonetti PO, Barsness GW, Keelan PC, Schnell TI, Pumper GM, Kuvin JT, Schnall RP, Holmes DR Jr., Higano ST, Lerman A. **Enhanced External Counter-Pulsation Improves Endothelial Function in Patients with Symptomatic Coronary Artery Disease.** *JACC* 2003;41:1761-8
42. Itzhaki S, Dorcin H, Clark G, Lavie L, Lavie P, Pillar G. **One-year treatment with a Herbst mandibular advancement splint improves Obstructive Sleep Apnea and endothelial function.** *SLEEP* 2006; 29 (Suppl.):A164 (480)
43. Pillar G. **Oral appliance improves Sleep Apnea and Endothelial Function.** *OTO* 2007
44. Itzhaki S, Pillar G, Lavie P, Lavie L. **Endothelial function of patients with Obstructive Sleep Apnea improves following 3 months on CPAP.** *SLEEP* 2006; (Suppl.):A164
45. Morgenthaler T, Lerman A. **Endothelial Dysfunction Assessed By Peripheral Arterial Tonometry In Obstructive Sleep Apnea Patients Improves With CPAP Therapy.** *SLEEP* 2005; 28 (Suppl.):A177
46. Hsu LL, Ataga KI, Nwose OM, Kakkis E. **Peripheral Arterial Tonometry Assessment of Endothelial Dysfunction in Sickle Cell Patients (For the 6R-BH4 in Sickle Cell Disease Study Group).** *American Society of Hematology* 2008; 2496
47. Prince WT, Stewart Campbell A, Tong W, Sweetnam P, Rosen R, Goldstein I, Willett MS, Roesch BG, Garcia WD. **SLx-2101, A New Long-Acting PDE5 Inhibitor: Preliminary Safety, Tolerability, Pharmacokinetics and Endothelial Function Effects in Healthy Subjects.** *SMSNA* 2005
48. Aversa C, Vitale M, Volterrani A, Fabbri G, Spera M, Fini G, M. C. Rosano. **Chronic administration of Sildenafil improves markers of endothelial function in men with Type 2 diabetes.** *Diabetic Medicine*; 25: 37-44
49. Yeo TW, Lampah DA, Gitawati R, Tjitra E, Kenangalem E, McNeil YR, Darcy CJ, Granger DL, Weinberg JB, Lopansri BK, Price RN, Duffull SB, Celermajer DS, Anstey NM. **Impaired nitric oxide bioavailability and L-arginine-reversible endothelial dysfunction in adults with falciparum malaria.** *Journal of Experimental Medicine* 2007; 204: 2693-2704
50. Yeo TW, Lampah DA, Gitawati R, Tjitra E, Kenangalem E, McNeil YR, Darcy CJ, Granger DL, Weinberg JB, Lopansri BK, Price RN, Duffull SB, Celermajer DS, Anstey NM. **Recovery of Endothelial Function in Severe Falciparum Malaria: Relationship with Improvement in Plasma L-Arginine and Blood Lactate Concentrations.** *J Infect Dis.* 2008; 198(4):602-608
51. Thum T, Schmitter K, Fraccarollo D, Jakob M, Werthmann R, Bunemann M, Ertl G, Bauersachs J. **Deleterious effects of aldosterone on human endothelial progenitor cells are protein kinase A-mediated and can be prevented by mineralocorticoid receptor blockade.** *EHI* 2007; 28 (Suppl.):478
- 52 - Luu LJ, Willoughby SR, Cameron JD, Nelson AJ, Worthley SG, Worthley MI. **One Week of Clopidogrel Improves Endothelial Function in Subjects with Stable Coronary Artery Disease: A Randomized Control Study.** *ACC* 2009



Reliable & Reproducible

Noninvasive

Immediate and automatic test analysis

User independent

Easy to use

FDA cleared  
CE marked

Operated by nurse/technician



**itamar**

Itamar Medical

**Itamar Medical Ltd.**  
 9 Halamish St.,  
 P.O.Box 3579  
 Caesarea 38900, Israel  
 Tel + 972 4 617 7000  
 Fax + 972 4 627 5598

**Itamar Medical Inc.**  
 160 Speen St.  
 Suite 201  
 Framingham  
 MA 01701-2003, USA  
 Tel 1 888 748 2627

**www.itamar-medical.com**  
**info@itamar-medical.com**