Endothelial Function Assessment in Patients with Erectile Dysfunction

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**ABSTRACT:** Background: Erectile dysfunction (ED), a common problem in males of all ages, can be of organic, psychogenic or combined etiology. Organic ED is mainly caused by vascular and neurological disorders. One of the available tests for differentiating organic from inorganic ED is measuring penile tumescence and rigidity during the REM phase of sleep. However, this test lacks the ability to differentiate between a vascular and non-vascular cause of organic ED.

**Objectives:** To compare the results of the EndoPAT test and the nocturnal penile tumescence (NPT) test in patients with erectile dysfunction.

**Methods:** Twenty patients with ED were recruited for the study. Each participant was evaluated by the SHIM score, RigiScan during polysomnography, and two EndoPAT tests (at the beginning and end of the study).

**Results:** Seventeen patients had a SHIM score ≤ 21; 4 of them had organic ED with a mean EndoPAT score of 1.49, significantly lower than the 1.93 mean EndoPAT score of the 11 patients in the psychogenic ED group (P = 0.047). Two participants had a neurological impairment (spinal trauma and herniated disk). The average SHIM score in the vascular organic group was 6.25 points as compared to 11.69 for the psychogenic group (P = 0.027). The positive predictive value was 43% and the negative predictive value 90%.

**Conclusions:** EndoPAT could be helpful in excluding organic ED.

**KEY WORDS:** EndoPAT, endothelial function, erectile dysfunction (ED), RigiScan, SHIM score, nocturnal penile tumescence (NPT)

**E**rection is a complex process involving neurological, vascular, endocrinologic and psychological factors [1]. Erectile dysfunction (ED), which affects all age groups, is the most common sexual problem in men, with an overall prevalence of 16% [1]. ED is defined as a consistent or recurrent inability to attain and/or maintain an erection sufficient for intercourse [2]. Up to 7% of men aged 18–69 years suffer from ED [3], while more than 75% of men older than 80 years have this condition [4]. The prevalence in Israel was shown to be as high as 25% in military men aged 25–55 [5]. There are numerous proven etiologies for ED, generally classified as organic (such as vascular, neurological, hormonal disorders) or psychogenic [6]. Common risk factors for ED and vascular diseases have been observed, including atherosclerosis, diabetes of any type, obesity, smoking, hypercholesterolemia and metabolic syndrome [7]. Indeed, increasing evidence proves that ED can be an early manifestation of arterial diseases [8]. The penile endothelium plays a major role in the erection process by producing nitric oxide (NO), a factor responsible for the dilation of the penile artery, relaxation of the corpus cavernosa and consequently erection. Thus, dysfunction of the penile endothelium, as found in some disorders, might play an important role in the pathophysiology of ED [9].

Assessment of endothelial function can be accomplished using several techniques, one of which is measuring the finger arterial pulse wave amplitude using EndoPAT [10]. Being also endothelial tissue, there is a correlation between finger endothelial function and penile endothelial function [11].

The nocturnal penile tumescence (NPT) test can differentiate between organic and psychogenic ED by assessing sleep-time erections. Every male should normally experience spontaneous erection during the REM phase of sleep [12]. If nocturnal erections are of adequate duration and strength, then the etiology is probably inorganic [13]. However, the NPT test has a low diagnostic accuracy of less than 76% [14]. Moreover, the NPT test does not have the ability to differentiate between vascular and non-vascular organic etiologies; therefore, coupling the two tests can help achieve the right diagnosis.

The purpose of our study was to test the correlation between endothelial performance and erectile function in patients suffering from ED by comparing the results of the EndoPAT test and the NPT test during night sleep monitored by polysomnography. Establishing such a correlation can improve our understanding of ED and help physicians in the diagnosis and treatment of ED.

**PATIENTS AND METHODS**

Between August 2007 and March 2008 we recruited 20 patients for our study. All patients were older than 18 years, suffered...
from ED and were referred to the sleep lab for the NPT test. Patients on alpha-blocker treatment were excluded because of its apparent effects on endothelial and erectile functions. The study was approved by the local institutional review board, and all participants signed an informed consent form.

ED EVALUATION
ED was evaluated with the Sexual Health Inventory for Men (SHIM) score, RigiScan during polysomnography, and EndoPAT. SHIM score is the main tool for assessing patients with ED and has a 73.8% overall accuracy for detecting and classifying ED. It is based on a questionnaire [Appendix 1] that includes five questions; each has a score of 0–5, except for question 1 that has a score of 1–5. This questionnaire is based on the International Index of Erectile Function (IIEF). The total score ranges are 1–25 and are calculated by adding the score of each question. A total score of ≤ 21 defines ED [15].

RIGISCAN FOR NPT TESTING
RigiScan (Dacomed Corporation, Minneapolis, MN, USA) is a portable device that can continuously monitor penile radial rigidity, penile tumescence, and number and duration of erections. The device consists of a recording unit placed and affixed to the patient’s thigh and connected to a computer that records the data and presents it in graphic and numeric forms. Attached to this unit are two loops: one is placed at the base of the penis and the other at the coronal sulcus (the penile tip). The device records penile tumescence and rigidity by calculating increased circumference and constriction of the loops, respectively. Constriction of the loops occurs every 3 minutes, applying a radial compression force of 2.8N. If the base loop registers a circumference increase of more than 10 mm, sampling frequency is increased to every 30 seconds [16]. This test is conducted during the polysomnographic sleep test in order to observe and eliminate false-positive results due to fragmented sleep [14].

A normal test is defined as one or more erection episodes during the night, with a minimum circumference increase of 3 cm at the penile base and 2 cm at the penile tip, with a rigidity of ≤ 70% lasting at least 10 minutes [17].

POLYSOMNOGRAPHIC SLEEP TEST
For each participant, electrodes were attached at arrival and sleep was monitored from 10 p.m. to 6 a.m., using a computerized PSG system (Embla Flaga hf, Iceland). Sleep monitoring and staging were done using standard electroencephalographic (EEG) (C3-A2 and O2-A1), electromyelographic (EMG), and electro-oculographic (EOG) techniques. During sleep studies, the following parameters were monitored and recorded: nasal or oral airflow (thermistor), chest and abdominal wall motion (piezo electrodes), electrocardiography (ECG), lower limb movements, and arterial oxygen saturation. All studies were scored by an experienced PSG technologist.

ENDOPAT 2000 DEVICE
EndoPAT (Itamar Medical Ltd, Caesarea, Israel) is a non-invasive device that uses pneumatic probes to measure and record finger arterial pulse-wave amplitude (PWA) in a beat-to-beat manner. A finger probe is placed on the index of each hand, and the peripheral arterial tone (PAT) is recorded from both hands throughout the study. Endothelial function is assessed using the reactive hyperemia technique, based on the fact that normal reactive hyperemia correlates with normal endothelial function and NO release.

With the patient sitting in a comfortable chair with both hands placed on the chest, baseline measurements are obtained for 5 minutes with the patient at rest, followed by another 5 minutes of measurement with one arm occluded by inflating a cuff on the patient’s upper arm until it reaches suprasystolic pressure (50 mmHg above systolic pressure) and then released to induce reactive (flow-mediated) hyperemia, which is measured for another 5 minutes. The other hand remains free, with no external pressure, as a reference for correction of potential systemic changes. The endothelial function score is calculated by dividing the mean post-occlusion PWA to the mean pre-occlusion PWA of the tested arm corrected to the control arm. A ratio < 1.67 is considered an abnormal test and defines impaired endothelial function and NO release [10,11].

STUDY DESIGN
After a thorough explanation, patients were asked to complete the SHIM questionnaire and provide other relevant data including past medical history, medications, height, weight, neurologic impairment, age and smoking habits.

Each study started with the endothelial function test using the EndoPAT. Thereafter, patients went to sleep in the sleep lab for one night while connected to the RigiScan device and to the polysomnograph. On the following morning after awakening, patients underwent another EnD test in order to eliminate the potential effects of cigarettes, food and caffeine on the study results.

ANALYSES
Using Student’s t-test, we compared the NPT and EndoPAT results between the organic and psychogenic groups. We hypothesized that vascular organic (non-neurologic) ED patients demonstrate impaired EndoPAT results, as compared to those with non-vascular organic (neurogenic/psychogenic) ED patients, who should have normal EndoPAT results. Statistical significance was defined as P < 0.05. Statistical analyses were performed using SPSS v21.

RESULTS
Of the 20 participants, 17 had a SHIM score ≤ 21 and were considered the study group; the remaining 3 participants
were excluded from the analyses. NPT tests showed that 11 patients had inorganic ED and 6 had a presumably organic ED. However, two of the six patients with organic ED had a neurological impairment (spinal trauma and herniated disk), which could better explain their ED than endothelial dysfunction since both of them had no apparent risk factors for endothelial dysfunction. Baseline characteristics are summarized in Table 1.

We grouped the patients into three groups based on the NPT test and medical history: (i) vascular organic ED group of 4 patients, (ii) non-vascular organic ED group of 2 patients with neurologic ED, and (iii) the inorganic (psychogenic) ED group of 11 patients.

Our results showed a significant difference between evening and morning EndoPAT scores. We decided to use the morning results for analyses as it would be more accurate and not affected by caffeine or cigarettes.

The mean EndoPAT score of four patients in the vascular organic ED group was 1.49 points, significantly lower than 1.93 points for the 11 patients in the psychogenic ED group (P = 0.047). There was no significant difference between the EndoPAT scores of psychogenic and neurogenic ED patients.

The average SHIM score for the vascular organic group was 6.25 points compared to 11.8 points for the psychogenic group (P = 0.027). Comparing the SHIM scores of psychogenic ED patients with those of neurogenic ED patients revealed no significant difference (P = 0.06). Data are summarized in Table 2 and Figure 1.

All patients in the organic ED group suffered from hypercholesterolemia and diabetes mellitus (three patients with type 2 DM and one with type 1 DM). However, only two patients from the psychogenic ED group (normal NPT and EndoPAT tests) had type II DM. Two patients with organic

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**Table 1. Patients’ characteristics**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Neurologic impairment</th>
<th>Age (years)</th>
<th>Smoking history (PY)</th>
<th>Diabetes mellitus</th>
<th>Other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>56</td>
<td>No</td>
<td>Type 2</td>
<td>HTN, HL, IHD</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>62</td>
<td>No</td>
<td>Type 2</td>
<td>HTN, HL</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>46</td>
<td>27</td>
<td>Type 1</td>
<td>Leg amputation</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>40</td>
<td>10</td>
<td>Type 2</td>
<td>HTN, HLD</td>
</tr>
<tr>
<td>5</td>
<td>Spinal pelvic injury</td>
<td>38</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Herniated disk L2-L4</td>
<td>40</td>
<td>3.5</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>26</td>
<td>12</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>57</td>
<td>No</td>
<td>No</td>
<td>Asthma, HL, Crohn disease</td>
</tr>
<tr>
<td>9</td>
<td>Spinal surgery L4-L5</td>
<td>37</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>39</td>
<td>23</td>
<td>Type 2</td>
<td>HL</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
<td>28</td>
<td>7</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>Spinal surgery</td>
<td>32</td>
<td>4</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>Head trauma</td>
<td>56</td>
<td>1</td>
<td>Type 2</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>Pelvic trauma</td>
<td>41</td>
<td>6.5</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>Herniated disk L4-L5</td>
<td>44</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>Herniated disk L5</td>
<td>30</td>
<td>15</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>17</td>
<td>Head trauma</td>
<td>27</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

PY = cigarette-pack years, HTN = hypertension, HL = hyperlipidemia, IHD = ischemic heart disease

**Table 2. Mean EndoPAT score, SHIM score, age and BMI for each group**

<table>
<thead>
<tr>
<th></th>
<th>Vascular organic ED</th>
<th>Neurologic ED</th>
<th>Psychogenic ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>4</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>EndoPAT</td>
<td>1.49 (± 0.2)</td>
<td>2.37 (± 0.91)</td>
<td>1.93 (± 0.47)</td>
</tr>
<tr>
<td>SHIM</td>
<td>6.25 (± 3.77)</td>
<td>11 (± 8.48)</td>
<td>11.8 (± 4.44)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (± 9.86)</td>
<td>39 (± 1.41)</td>
<td>37.9 (± 10.94)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 (± 2.56)</td>
<td>32.2 (± 9.31)</td>
<td>26 (± 4.13)</td>
</tr>
</tbody>
</table>

Numbers are in mean with standard deviations in parentheses. ED = erectile dysfunction, BMI = body mass index

**Figure 1.** EndoPAT results (Y axis) for each subject with the averages and standard deviation results for each group
EndoPAT is adequate for the initial screening of patients suspected to have vascular organic ED compared to those with inorganic ED.

Our data show that EndoPAT can be used for excluding organic ED since it has a high negative predictive value (NPV) of 90%. However, it has a low positive predictive value (PPV) of 43%, which means that it cannot be used for ED diagnosis [Table 3]. Patients with a normal EndoPAT test had a very low likelihood of being diagnosed with vascular organic ED. Patients with ED whose EndoPAT test was negative and had no other apparent risk factors for ED (e.g., neurological impairment, surgery) can be assumed to have psychogenic ED.

Being a low cost, easy-to-perform and relatively short test, EndoPAT is adequate for the initial screening of patients suspected of having ED and with no apparent neurological pathology. Patients who have a positive EndoPAT result are referred to the NPT test for definitive diagnosis, and those with negative results can be considered as having psychogenic ED.

In our study there were four patients with false-positive EndoPAT results. All four were smokers and suffered from hyperlipidemia. Several previous studies showed that smoking [18,19] and hyperlipidemia [20] causes systemic endothelial dysfunction and may cause organic ED. Most probably, these positive results demonstrate the patients’ preliminary systemic endothelial dysfunction (caused by these risk factors), but without apparent ED (therefore, a negative NPT result). Smoking cessation [21] and lipid level reduction [22] may improve endothelial function, erection, and subjective indices of erectile function [23].

Another well-known risk factor for organic ED is diabetes mellitus [24]. In our study, all patients in the organic ED group suffered from DM, with severe endothelial dysfunction (EndoPAT = 1.49) and very low SHIM score (6.25) as compared to the inorganic group. Since glycemic control improves systemic endothelial function [25], we need to encourage patients to strictly control their blood glucose levels.

We also found that patients with vascular organic ED had significantly lower SHIM score than patients with inorganic ED. Although predictable and logical, this finding could be used to help define the diagnosis by SHIM score and EndoPAT alone in patients suspected of having vascular organic ED. However, a large study should be conducted to better address this question.

We are aware of the limitations of this study, the most important being the small patient number. Another is limited diagnostic accuracy of the gold standard test (RigiScan NPT testing) for differentiating organic from psychogenic ED. Moreover, there is a large between-group difference in age and comorbidities that could affect the results. This problem could have been avoided by a better selection of patients.

**CONCLUSIONS**

These initial results on the use of EndoPAT for the diagnosis of vascular organic ED are promising. Although we could not demonstrate its usefulness for diagnosing vascular organic ED, we could clearly show its high accuracy in excluding this diagnosis.

**Table 3. Statistical measures for the effectiveness of EndoPat in the diagnosis of ED as compared to the gold standard NPT test**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>75% (20–96%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>69% (39–91%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>43% (10–81%)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>90% (55–98%)</td>
</tr>
</tbody>
</table>

NPT = nocturnal penile tumescence

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**References**


Capsule

Selective small-molecule inhibition of an RNA structural element

Riboswitches are non-coding RNA structures located in messenger RNAs that bind endogenous ligands, such as a specific metabolite or ion, to regulate gene expression. As such, riboswitches serve as a novel, yet largely unexploited, class of emerging drug targets. Demonstrating this potential, however, has proven difficult and is restricted to structurally similar antimetabolites and semi-synthetic analogues of their cognate ligand, thus greatly restricting the chemical space and selectivity sought for such inhibitors. Howe et al. report the discovery and characterization of ribocil, a highly selective chemical modulator of bacterial riboflavin riboswitches, which was identified in a phenotypic screen and acts as a structurally distinct synthetic mimic of the natural ligand, flavin mononucleotide, to repress riboswitch-mediated ribB gene expression and inhibit bacterial cell growth. These findings indicate that non-coding RNA structural elements may be more broadly targeted by synthetic small molecules than previously expected.

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Eitan Israeli

Capsule

A naturally occurring variant of the human prion protein completely prevents prion disease

Mammalian prions, transmissible agents causing lethal neurodegenerative diseases, are composed of assemblies of misfolded cellular prion protein (PrP). A novel PrP variant, G127V, was under positive evolutionary selection during the epidemic of kuru – an acquired prion disease epidemic of the Fore population in Papua New Guinea – and appeared to provide strong protection against disease in the heterozygous state. Asante and co-workers investigated the protective role of this variant and its interaction with the common, worldwide M129V PrP polymorphism. V127 was seen exclusively on a M129 PRNP allele. We demonstrate that transgenic mice expressing both variant and wild-type human PrP are completely resistant to both kuru and classical Creutzfeldt-Jakob disease (CJD) prions (which are closely similar) but can be infected with variant CJD prions, a human prion strain resulting from exposure to bovine spongiform encephalopathy prions to which the Fore were not exposed. Notably, mice expressing only PrP V127 were completely resistant to all prion strains, demonstrating a different molecular mechanism to M129V, which provides its relative protection against classical CJD and kuru in the heterozygous state. Indeed, this single amino acid substitution (GV) at a residue invariant in vertebrate evolution is as protective as deletion of the protein. Further study in transgenic mice expressing different ratios of variant and wild-type PrP indicates that not only is PrP V127 completely refractory to prion conversion but acts as a potent dose-dependent inhibitor of wild-type prion propagation.

Nature 2015; 522: 478
Eitan Israeli

“My entire soul is a cry, and all my work is a commentary on that cry”

Nikos Kazantzakis (1883-1967), Greek writer and philosopher, celebrated for his novel Zorba the Greek