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The neuropathy of erectile dysfunction

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These studies were intended to explore the relationship between autonomic neuropathy and erectile dysfunction (ED). Sensory thresholds reflecting the integrity of both large diameter, myelinated neurons (ie pressure, touch, vibration) and small diameter axons (ie hot and cold thermal sensation) were determined on the penis and finger. Data were compared across subjects with and without ED, controlling for age, hypertension and diabetes. The correlation of specific thresholds scores and IIEF values were also examined. Seventy-three patients who visited the academic urology clinics at Montefiore hospital were evaluated. All patients were required to complete the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire: 20 subjects had no complaints of ED and scored within the 'normal' range on the IIEF. Patients were subsequently tested on their index finger and glans penis for vibration (Biothesiometer), pressure (Semmes-Weinstein monofilaments), spatial perception (Tactile Circumferential Discriminator), and warm and cold thermal thresholds (Physitemp NTE-2). Sensation of the glans penis, as defined by the examined sensory thresholds, was significantly diminished in patients with ED and these differences remained significant when controlling for age, diabetes and hypertension. In contrast, thresholds on the index finger were equivalent in the ED and non-ED groups. Threshold and IIEF scores were highly correlated, consistent with an association between diminished sensation and decreasing IIEF score (worse erectile functioning). These relations also remained significant when controlling for age, diabetes and hypertension. The findings demonstrate dysfunction of large and small diameter nerve fibers in patients with ED of all etiologies. Further, the neurophysiologic measures validate the use of the IIEF as an index of ED, as objective findings of sensory neuropathy were highly correlated with worse IIEF scores. The sensory threshold methods utilized represent novel, non-invasive and relatively simple procedures, which can be used in a longitudinal fashion to assess a patient's neurological response to therapies.
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Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. The prevalence in the USA is 10–20 million men.[1] The male erectile response is a neurovascular event reliant on the complex interaction between neurological and vascular responses.[1,2] Erectile dysfunction is multifactoral and has been typically classified by the primary presumed cause: vasculogenic, psychogenic, neurogenic and endocrinologic disease. Any condition or injury that impairs the transmission of impulses along the psychogenic or reflexogenic neurological pathway, may be associated with neurogenic erectile dysfunction.[3]

The penis is innervated by the dorsal penile and perineal nerves.[4] These nerves are a continuation of sympathetic and parasympathetic autonomic nerves as well as sensory and motor somatic nerves.[2] The somatic sensory system is responsible for the specialized structures that transmit information about the external environment. There are four major classes of somatic sensation: pain, temperature, position sense and touch-pressure sensation.[5] These stimuli are transmitted in the autonomic nervous system through both large (Aα and Aβ) and small (Aδ and C) caliber nerves.[5,6]

Currently, many tests are available to evaluate the sensory afferent nerves from the penile skin, as well

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as the motor efferent nerves to the perineum. These tests include the bulbocavernosus reflex, penile thermal sensory threshold measurement, corpus cavernosum electromyogram (CC-EMG) signal assessment, somatosensory evoked potentials, anal or urethral sphincter EMG, and vibration perception sensitivity.[2,6–12] The problems with many of these tests is that they tend to be complex, time-consuming, and do not directly measure autonomic function or correlate with the degree of ED.

This study was designed to test the hypothesis that autonomic neuropathy is a significant component of ED and, further, that this deficit can be evaluated by measuring specific aspects of sensation in the nerves innervating the penis. This study was also designed to evaluate the impact of age and concomitant medical conditions, such as diabetes, on the loss of cutaneous sensation of the penis.

Methods

All procedures were approved by the Institutional Review Board for the protection of human subjects in research at Montefiore Medical Center. A total of 73 patients from the Department of Urology participated in the study. These patients were recruited from December 2001 to February 2002. We believe that these subjects are a representative sample of the patients visiting the academic urology clinics; however no formal sampling strategy was utilized. Normal controls were sent for urological evaluation of problems not relating to erectile dysfunction, while other physicians typically referred patients with complaints of erectile dysfunction for evaluation at our clinic. Our patients comprised 37% Caucasians (27/73), 25% African Americans (18/73), 23% Hispanics (17/73), and 15% (11/73) unidentified. The demographics of the patients are presented in Table 1. Any person unable to understand English was excluded from participation. After consent was obtained, a medical history was recorded from each subject with a focus on any history of diabetes or hypertension. Patients were asked to complete the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire.[13,14] The IIEF is scored on a 1–30 scale; a score of 25 or greater represents no dysfunction, while a score less than 25 identifies those patients with erectile dysfunction.[13,14] In the cohort evaluated, 20 subjects (27.4%) scored within the normal range and constituted the no-ED group, while 53 subjects (73.6%) had evidence of ED by history (ED group). The battery of sensory evaluation was obtained in all subjects, with tests performed by the same researcher (CB). All sensory evaluations were performed on the palmar aspect of the distal right index finger. Additional measurements were recorded on the dorsal midline glans of the penis halfway between the coronal sulcus and the urethral meatus. In men who were not circumcised, the foreskin was retracted and the measurements were taken on the dorsal midline glans.

Table 1 Demographics of 73 patients

	No ED	*ED*
n	20	53
IIEF (mean)	28.4	13.4
Age ± s.d.	48.8 ± 15.0	55 ± 14.9
HTN	7 (35%)	20 (38%)
DM	2 (10%)	15 (28%)

All thresholds were obtained using a modified ascending method of limits or a two-alternative forced-choice procedure. Vibration was determined using a biothesiometer device (Bio-Medical Instrument Co., Newbury, OH, USA). Stimulus frequency was a fixed 120 Hz signal; intensity was roughly proportionate to the square of the applied voltage as measured by a sensitive galvanometer. As the voltage was gradually elevated, the subject identified the minimal energy at which he could distinguish between vibration and static touch.[12] Thresholds were recorded both from the palmer aspect of the distal right index finger and from the glans of the penis. All measurements were first performed on the finger, followed by the dorsal midline of the glans.

Sensitivity to touch was determined by use of the Semmes-Weinstein monofilament technique (North Coast Medical, Inc., Morgan Hill, CA, USA).[15,17] Briefly, subjects were contacted at the test site by a series of monofilaments of ascending intensity and threshold was defined as the smallest stimulus intensity correctly identified as a definite sensation of light pressure. Filaments were applied perpendicular to the skin for a period of approximately 1.5 s. The diameter of the filament (in millimeters), and therefore the intensity of the stimulation, increased from 2.83, 3.61. 4.31, 4.56, 5.07 to 6.65, which corresponds to an increase in target force of 0.07, 0.4, 2.0, 4.0, 10 and 300 g, respectively. The target forces of 0.07 and 0.4 g were repeated for a total of three trials before the higher intensities were examined successively. Thresholds were first determined on the palmar aspect of the right index finger and afterwards the glans.

Spatial threshold was determined using the tactile circumferential discriminator (Wyeth-Ayerst International Inc., Westtown, PA, USA). This device consists of a series of eight aluminum rods that vary in cross-sectional diameter and therefore in circumference from 12.5 to 40 mm.[16] The subject is initially presented with a reference rod (labeled 0) placed firmly agains the skin for a period of approximately 2 s and then with a 'test' rod (numbered 1–7) that differs in circumference. Threshold is determined as the smallest difference in circumference that can be

reliably detected on six consecutive trials. This procedure evaluates the spatial properties of sensation (ie minimal separation, number and distribution of activated receptors) and is similar to the measurement of two-point discrimination thresholds. Thresholds were again determined first on the index finger and then on the glans of the penis. A subject unable to differentiate between rod 7 and 0 was assigned the highest threshold (ie score of 8).

Hot and cold thermal thresholds were determined using a two-alternative forced-choice procedure[6,18,19] on both the penis and index finger. At each site the subject was presented with a thermal signal generated by a Physitemp NTE-2A Thermal Sensitivity Tester (Physitemp Instruments, Clifton, NJ, USA). Stimuli were presented against the skin using a hand-held thermal probe, capable of delivering both hot and cold temperatures over a 40°C temperature range. The probe was set to an acclimation temperature of 32°C[6,18,19] and all comparisons were made against this reference. The temperature was increased at increments of 1°C until the patient was able to correctly identify which temperature was warmer six times consecutively. That temperature was then recorded as the thermal threshold for warmth. The same procedure was followed for cold discrimination with the temperature decreased at increments of 1°C. In order to control for the possibility that any differences observed were due to differences in cutaneous temperatures between no ED and ED, surface skin temperature was measured at the test site in a subset of subjects. The assessment of thermal thresholds was labor-intensive and time-consuming. Not all subjects elected to participate in this assessment. Thermal thresholds were determined in a total of 36 subjects (28 with ED and eight without ED).

The following parameters were evaluated: age, history of diabetes, history of hypertension, measurement of tactile circumferential discrimination of the glans and finger, biothesiometry of the glans and finger, Semmes–Weinstein monofilament measurement of the glans and finger, warm temperature threshold of the finger and glans, cold temperature threshold of the finger and glans. Analysis for the tactile circumferential discriminator was performed both with the stated number and with the converted diameter in inches. Analysis for the SWM was also performed for both the labeled diameter of the filament and the corresponding value of force in grams. Univariate distributions were assessed for normality. Bivariate relationships were assessed using chi-square, *t*-test, and Pearson correlations. Composite null hypotheses were assessed with mixed models repeated measures analysis of variance using SAS PROC MIXED (version 8.1, 2001), allowing us to covary for age, diabetes and hypertension.

Results

The demographics of the 73 patients are presented in Table 1. The mean age was 48.8 (range 21–77) and 55.0 (range 22–81) for no ED and ED, respectively. Although the subjects with ED were slightly older, the age difference between groups was not significant ($P=0.12$). As expected, the IIEF score tended to be reduced (greater evidence of ED) as a function of age ($r=-0.14$), however the correlation was again not significant ($P=0.24$).

When measured at the glans of the penis, threshold values for each of the five sensory modalities evaluated were significantly increased (diminished sensation) in those with ED as compared with values of those with no ED (Table 2). For instance, the threshold for the detection of a stimulus as 'cold' was approximated 4.7°C lower (further from reference temperature) for ED group as compared with no ED ($P<0.0001$). Similarly, while a stimulus was perceived as 'warm' when it was an average of 3.8°C above the reference temperature in subjects without ED, it needed to be more than 7.6°C above reference to be detected as 'warm' in the subjects with ED. Modalities associated with both small diameter axons (ie temperature) and large diameter axons (ie pressure, vibration, spactial threshold) were all sharply different across groups. The differences in mean values at the penis across groups remained significant for each of the neurophysiologic measures (except vibration, $P<0.06$), even after controlling for age, diabetes and hypertension.

Table 2 Mean ± s.e.m. neurophysiological testing values for the glans penis

	*Tactile circumferential discriminator**	*Semmes–Weinstein monofilaments*†	*Biothesiometer*†	*Cold threshold*†	*Warm threshold*†
No ED	4.80 ± 0.42	0.90 ± 0.24	3.95 ± 0.40	29.1 ± 0.55	35.8 ± 0.45
ED	6.52 ± 0.23	3.54 ± 0.44	7.72 ± 0.80	24.4 ± 0.38	39.6 ± 0.35

*$P = 0.001$; †$P = 0.0001$.
TCD values are the labeled number. The monofilament values are the diameter of the monofilaments converted into the corresponding target force in grams. The *P*-values remained significant for the monofilaments when analysis was performed for reported monofilament diameter. The biothesiometer measurement is the relative value stated on the biothesiometer. The warm and cold thresholds are reported in °C.

The deficit in sensory function was consistently greater in patients with worse ED, resulting in a highly significant correlation between each of the five neurophysiological measurements of the penis and the patient's IIEF score (Table 3). Each of the correlations was in the expected direction (Table 3). The correlation of each measure and IIEF scores also remained significant after controlling for age, diabetes and hypertension ($P < 0.05$).

Since resident skin temperature may have an effect on cutaneous sensation, especially thermal thresholds, we examined the surface temperature of the skin overlying the glands in a limited random sample of subjects in no ED and ED groups. The mean temperature in subjects without ED was 31.8°C ($n = 2$), and is not distinguishable from the mean cutaneous temperature of the glans in patients with erectile dysfunction (31.9°C, $n = 11$).

In contrast to the results obtained at the penis, there were no significant differences between no ED and ED groups in cutaneous sensory thresholds measured at the finger (Table 4). Only one measure, warm threshold, strongly trended in the direction of decreased function in subjects with ED ($P = 0.07$). In addition, there was no significant correlation between any of the five thresholds examined at the finger and patient's IIEF scores.

Diabetes and hypertension, as well as age, may also influence sensation. The prevalence of hypertension was similar across groups. Of those patients with a history of hypertension 74.1% also reported erectile dysfunction compared with 71.7% of the population without ED. Regression models using age, hypertension and diabetes as covariates demonstrated that hypertension, for all neurophysiologic measurements of both the penis and finger, was not significant, indicating that hypertension does not contribute to the results obtained. Of those patients with a history of diabetes, 88.2% also reported erectile dysfunction as compared with 67.9% of the population who reported no history of diabetes. There was a significant contribution (based on regression analysis) associated with diabetes and measurements of vibration at the penis ($P = 0.003$). We also demonstrated a significant contribution by diabetes to warm threshold ($P = 0.04$) at the penis and to tactile circumferential discriminator at the finger ($P = 0.04$). Although diabetes contributed significantly to vibration and warm threshold at the penis, its impact on these measurements did not outweigh the overall differences between those with ED and normal controls. Age is a third subject variable that might alter sensory thresholds. As expected, in the present study there was a significant correlation between increasing age and worsening cutaneous sensation of the finger to vibration, pressure and spatial resolution (based on regression analysis ($P < 0.05$)). However, age was not significantly correlated with warm and cold thresholds. Of the penis measurements, age is only significantly correlated with vibration sensation ($P < 0.05$). Again, the contribution of age towards the cutaneous measurements did not obscure the overall differences between those patients with ED and normal controls.

Table 3 Pearson coefficients of the glans penis and IIEF score

	*TCD**	*SWM**	*Biothesiometer**	*Cold threshold**	*Warm threshold**
Glans *r* value	− 0.48	− 0.38	− 0.35	0.60	− 0.58

*$P < 0.005$.

Discussion

Impaired blood flow to the penis is the most common cause of ED. While altered neural function is generally regarded as a second critical component of ED, this factor is difficult to assess and its contribution may therefore be underestimated. Both the dorsal penile and perineal nerves contain a variety of axons that differ in cross-sectional diameter and the presence and degree of myelin. A careful consideration of the impact of neural deficits on erectile function must differentiate between activities conducted in small diameter fiber pathways (ie Aδ and unmyelinated C fibers) and activity conveyed in relatively large diameter, myelinated fiber systems (Aα and Aβ). The assessment of sensory function provides a non-invasive means of assessing the integrity of the neural innervation of

Table 4 Mean ± s.e.m. neurophysiological testing values for the finger

	Tactile circumferential discriminator	*Semmes–Weinstein monofilaments*	*Biothesiometer*	*Cold threshold*	*Warm threshold*
No ED	2.55 ± 0.30	0.29 ± 0.02	3.51 ± 0.30	30.1 ± 0.52	34.0 ± 0.33
ED	2.65 ± 0.23	0.27 ± 0.04	4.02 ± 0.30	29.4 ± 0.34	35.0 ± 0.45

TCD values are the labeled number. The monofilament values are the diameter of the monofilaments converted into the corresponding target force in grams. The *P*-values remained non-significant for the monofilaments when analysis was performed for reported monofilament diameter. The biothesiometer measurement is the relative value stated on the biothesiometer. The warm and cold thresholds are reported in °C.

the penis, and the evaluation of multiple modalities affords the ability to differentiate function within specific axon types, for instance, the determination of absolute threshold for the detection of vibration measures transduction and conduction of activity in relatively large diameter, myelinated axons, while the assessment of thermal thresholds provides an index of activity in unmyelinated C fiber pathways (warm) and small myelinated Aδ fibers (cold).

In recent years, quantitative sensory testing (QST) has emerged as an important adjunct of the neurologic examination and its use has been recommended by several consensus panels including the American Neurologic Association, the American Diabetes Association and the Peripheral Nerve Society. A variety of QST instruments and testing algorithms have been developed and utilized to provide standardized, non-invasive and semi-objective measures of neural function. These procedures have proven valuable in tracing the onset and progression of peripheral neuropathy associated with aging, disease, exposure to exogenous neurotoxins and in documenting iatrogenic neuropathies associated with the treatment of cancer and HIV infection.[16,20–26] Validated equipment and procedures exist for the testing of vibration, pressure, spatial perception, warm, cold and painful stimuli. The approach is to provide well-controlled, standardized sensory stimuli and to evaluate detection threshold using established psychophysical procedures, such as ascending method of limits, and two alternative forced choice.[27,28] For instance, a simple hand-held device, the Semmes–Weinstein monofilament, has been found to be a valuable method of screening for deficits in pressure sensation,[1517,21] while the Tactile Circumferential Discriminator has been used to screen for neuropathy and foot ulcer risk.[16,22]

While most tests of QST have focused on sensation in the hands and/or feet, a few studies have used its approach to evaluate sensation in the genital region. Romanzi *et al* found that Semmes–Weinstein monofilaments could be used to evaluate pressure/touch sensitivity of the female external genitalia and various devices have been used to measure vibration thresholds at the penis.[12,17,29,30] A recent review of 13 studies on vibrotactile penile thresholds found that threshold levels increased as a function of age and that penile thresholds of men with ED were significantly higher (diminished sensitivity) than age-controlled functional males.[30] Yarnitsky *et al* found that penile thermal thresholds could be used as a repeatable, valid diagnostic tool to evaluate somatic small fiber function and reported normative values.[18] Lefaucheur expanded the use of penile thermal thresholds, and demonstrated higher thresholds in impotent diabetic males.[19]

The results of the present study greatly expand the use of QST in the evaluation of neural function at the penis and provide unique information about the correlation of sensory function and ED. To our knowledge, the present study is the first to apply this technique for the evaluation of the neurophysiology of the penis. Specifically these results confirm that patients with ED, regardless of etiology, have broad-based (not unique to one neural fiber group) deficits detected with multiple modalities and testing procedures when compared with normal controls. We are the first group to utilize pressure (Semmes–Weinstein monofilaments) and spacial perception (the Tactile Circumferential Discriminator) for assessing neuropathy of the penis and demonstrate increased thresholds (worse functioning) for patients with complaints of ED. We further confirmed large fiber axonal dysfunction with increased vibration (Biothesiometer) thresholds in patients with ED. We are the first to assess small fiber axonal function with warm and cold thermal thresholds (Physitemp NTE-2) in non-diabetic patients with ED and demonstrate worse functioning when compared with normal controls.

Our results suggest that neuropathy at the penis exists in all forms of erectile dysfunction including arterial and venous disease. Additionally, in some cases (eg diabetes) dysfunction of the penile nerves antecedes deficits in cutaneous function detected at the finger (general neuropathy). This leads us to believe that in cases such as diabetes there may be a different underlying cause for the erectile dysfunction than the classically taught chronically progressive, length-dependent, distal axonopathy of the dying-back type.[31] Since neurologic erectile dysfunction may be related to multiple causes including chronic diseases (eg diabetes mellitus, multiple sclerosis, Parkinson's disease, Alzheimer's disease), surgery or trauma (eg radical retropubic prostatectomy, herniated lumbar disk), and neural malformation (spina bifida) to name a few, multiple factors may be responsible for the neurological defects that we see in our study.[2] Loss of sensation may be related to a change in fiber density (loss of axons — distal axonopathy), deficits in transduction (generator potential), deficits in conduction (velocity synchrony), or non-structural defects such as redistribution of ion channels. The exact mechanism of neuropathy remains to be elicited in future research.

In order to determine which patients had erectile dysfunction, all participants were required to complete the erectile function domain of the IIEF. This test has been widely used by the pharmaceutical industry to assess the outcomes of drug therapy through non-invasive, self-assessment questionnaires. The erectile function domain of the IIEF has been validated in multiple studies as a reliable test, not only for determining which patients have ED, but also for assessing the severity of function.[13,14,32,33] Despite its widespread use in clinical trials assessing function before and after medical intervention, to our knowledge, only one group has

tried to compare the IIEF to current erectile dysfunction testing.[34] Blander *et al* demonstrated that the IIEF score did not differentiate between the specific etiologies of ED as determined by penile blood flow studies and testing with prostaglandin E_1. Additionally, some patients with normal prostaglandin E_1 testing had low IIEF scores of 13/25.[34] In contrast to their study, we found a significant correlation between the IIEF score (encompassing patients with all forms of erectile dysfunction) and neurophysiological measurements of touch, pressure, vibration and thermal discrimination. This suggests that the IIEF may be a good questionnaire to assess the neurological component of erectile dysfunction.

While our study provides several insights into the neuropathy of ED, our study is limited by both the sample and the methods of QST. We chose to use a sample of patients from the academic urology offices. These patients may not be representative of the normal population or the population of individuals seen in a typical medical or primary care clinic. In order to improve our understanding of normal penile aging and function, as well as provide accurate confidence intervals for cut-off scores defining ED, a larger normal population from the general population should be obtained. While QST is non-invasive, easy to perform in an office setting, reproducible and well suited for multicenter trials, it does have some limitations.[20,23,27] QST is a psychophysical test and requires the cooperation, attention and motivation of the patient.[20,27] It has been typically used for the detection of peripheral neuropathy in diabetic patients, but it captures information from the peripheral receptors which must be processed centrally and therefore requires integrity of the entire neural pathway (ie pathology anywhere along the way may affect results).[20,27] While QST has limitations, our results remained consistent with the literature. We demonstrated a significant correlation between age and Semmes–Weinstein monofilament testing and tactile circumferential discriminator of the finger, which are consistent with cutaneous pressure threshold and two-point discrimination studies which demonstrate a deterioration with aging.[35–37] Our vibrotactile penile thresholds were also in agreement with a recent review of 13 studies which found that threshold levels increased as a function of age and that penile thresholds of men with ED were significantly higher than age-controlled functional males.[30] Our measurements of cold threshold of the finger are in agreement with a study by Gelber *et al*, who looked at cold temperature thresholds of the dominant finger and found no association between thermal perception thresholds and age.[23] Finally, in agreement with Lefaucheur *et al*, we found that there was a significant difference with both warm and cold thresholds when comparing those with ED and normal controls at the penis.[6]

We evaluated the functional integrity of the penile autonomic nervous system in patients with erectile dysfunction. We demonstrated dysfunction of the large ($A\alpha$ and $A\beta$) caliber fibers with significant differences between normal controls and ED patients with pressure, spatial perception, and vibration. We also demonstrated impairment in the small ($A\delta$ and C)-caliber nerves with significantly increased cold and warm thresholds in ED patients, and that, as men age, there is a significant loss of pressure and vibration sensitivity of both the glans penis and the finger. It also appears that the loss of vibration sensitivity is particularly significant for the diabetic patient.

Whether all of these changes are the end result of ED or the cause of erectile dysfunction remains to be elicited, but neuropathy appears to be a significant aspect of all forms of erectile dysfunction. These techniques give us a new way of assessing a patient's neurological response to therapies. They could be used in a longitudinal fashion to study changes over time in an office setting.

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