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QUANTITATIVE SOMATOSENSORY TESTING OF THE PENIS: OPTIMIZING THE CLINICAL NEUROLOGICAL EXAMINATION

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ABSTRACT

Purpose: Quantitative somatosensory testing, including vibration, pressure, spatial perception and thermal thresholds of the penis, has demonstrated neuropathy in patients with a history of erectile dysfunction of all etiologies. We evaluated which measurement of neurological function of the penis was best at predicting erectile dysfunction and examined the impact of location on the penis for quantitative somatosensory testing measurements.

Materials and Methods: A total of 107 patients were evaluated. All patients were required to complete the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire, of whom 24 had no complaints of erectile dysfunction and scored within the "normal" range on the IIEF. Patients were subsequently tested on ventral middle penile shaft, proximal dorsal midline penile shaft and glans penis (with foreskin retracted) for vibration, pressure, spatial perception, and warm and cold thermal thresholds.

Results: Mixed models repeated measures analysis of variance controlling for age, diabetes and hypertension revealed that method of measurement (quantitative somatosensory testing) was predictive of IIEF score ($F = 209$, $df = 4,1315$, $p < 0.001$), while site of measurement on the penis was not. To determine the best method of measurement, we used hierarchical regression, which revealed that warm temperature was the best predictor of erectile dysfunction with pseudo $R^2 = 0.19$, $p < 0.0007$. There was no significant improvement in predicting erectile dysfunction when another test was added. Using 37C and greater as the warm thermal threshold yielded a sensitivity of 88.5%, specificity 70.0% and positive predictive value 85.5%.

Conclusions: Quantitative somatosensory testing using warm thermal threshold measurements taken at the glans penis can be used alone to assess the neurological status of the penis. Warm thermal thresholds alone offer a quick, noninvasive accurate method of evaluating penile neuropathy in an office setting.

KEY WORDS: sensory thresholds, impotence, penis, sensitivity and specificity

Erectile dysfunction, defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance, has a reported prevalence of 10 to 20 million men in the United States.[1] The ability to have erections is reliant on the complex interaction among neurological, psychological and vascular responses.[1,2] The etiology of erectile dysfunction may be driven by a deficit in a single system but is often multifactorial. The assessment of this condition is a cardinal concern for the clinician. However, there are few objective, noninvasive measures capable of identifying subjects at risk for erectile dysfunction or staging the progression of the underlying physiological deficits.

Assessment of the contribution of dysfunction in the vascular system to erectile dysfunction has typically involved physical examination, penile plethysmography, dynamic infusion cavernosometry and cavernosography, intracavernous penile injection, duplex ultrasound and/or penile arteriography if indicated. The neurological evaluation generally involves the sensory afferent nerves from the penile skin, as well as the motor efferent nerves to the perineum. Available physiological tests are often somewhat invasive, complicated and time-consuming (for example the bulbocavernosus reflex, corpus cavernosum electromyogram, somatosensory evoked potentials).[2–9]

Recently, use of quantitative somatosensory testing (QST), which combines psychophysical methods and precise control of the type and magnitude of sensory stimulation, has been used successfully to evaluate the integrity of the somatic sensory system of the penis.[3,8,9] These procedures are noninvasive and relatively simple, and have the additional advantage that they can target dysfunction in large (that is vibration, touch) and small diameter sensory axons (that is temperature and pain).

A recent study by us exemplified this approach.[9] In this study 5 separate QST measures were evaluated at the penis, including temperature (warm and cold), vibration, pressure and spatial threshold. These measures were highly correlated with the erectile function domain of the International Index of Erectile Function (IIEF) in patients with erectile dysfunction of all etiologies. Although powerful, the battery of QST tests used in the previous study is impractical for routine clinical practice. The present study was designed to compare the sensitivity and specificity of each individual QST test in predicting erectile dysfunction and explore the impact of using single versus multiple tests for a screening evaluation. In addition, we examined the effects of location on the penis for QST in patients with and without erectile dysfunction.

METHODS

All procedures were approved by the Institutional Review Board at Montefiore Medical Center. A medical history was recorded which included diabetes and hypertension. The pro-

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cedures used have been described previously.[9] Briefly, each subject was evaluated with a portion of the QST procedures designed to determine response thresholds. The same researcher (C.B.B.) performed all tests. Thresholds were determined using either a modified ascending method of limits or a 2 alternative forced choice psychophysical algorithm.[10] Although multiple tests were performed in every subject, it was not possible to evaluate each modality and all recording sites in a single subject. The modalities and sites tested were randomly selected in an attempt to optimize the obtained information.

In most subjects measurements were recorded on the dorsal midline glans of the penis, halfway between the coronal sulcus and urethral meatus. In males who were not circumcised the foreskin was retracted and the measurements were taken on the dorsal midline glans. For all tests, except thermal thresholds, additional measurements were taken on the midline dorsal aspect of the penile shaft at the most proximal aspect and on the midline ventral aspect of the penile shaft, half the distance between the proximal base of the penis and the sulcus.

Sensory measures. Spatial perception threshold was determined using the tactile circumferential discriminator (Wyeth-Ayerst International Inc., Westtown, Pennsylvania). This device consists of a series of 8 aluminum rods that vary in circumference from 12.5 to 40 mm.[11] Threshold is determined as the smallest difference in circumference that can be reliably detected on 4 consecutive trials between the reference rod labeled O and the "test" rod (numbered 1 to 7). A subject unable to differentiate between rods 7 and 0 was assigned the highest threshold (that is score 8). This procedure evaluates the spatial properties of sensation (that is minimal separation, number and distribution of activated receptors) and is similar to the measurement of 2-point discrimination thresholds. Testing was done at the aforementioned locations.

Vibration was determined using a biothesiometer device (Bio-Medical Instrument Co., Newbury, Ohio). Stimulus frequency was a fixed 120 Hz. signal and intensity was roughly proportionate to the square of the applied voltage as measured by a sensitive galvanometer. As the voltage was gradually increased, the subject identified the minimal energy at which he could distinguish between vibration and static touch.[7] Thresholds were recorded in the aforementioned locations.

Sensitivity to touch was determined with the Semmes-Weinstein monofilaments (North Coast Medical, Inc., Morgan Hill, California).[11–13] 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 approximately 1.5 seconds. The intensity of the simulation increased in target force from 0.07 to 300 gm. The target forces of 0.07 and 0.4 gm. were repeated for a total of 3 trials before the higher intensities were examined successively. Thresholds were determined at the aforementioned locations.

Hot and cold thermal thresholds were determined using a 2 alternative forced choice procedure[10] on the glans penis. At each site the subject was presented with a thermal signal generated by a Physitemp NTE-2A Thermal Sensitivity Tester (Physitemp Instruments, Clifton, New Jersey). Stimuli were presented against the skin using a hand-held thermal probe. The probe was set to an acclimation temperature of 32C,[3,8] and all comparisons were made against this reference. The temperature was increased at increments of 1C until the patient was able to identify correctly which temperature was warmer 4 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 1C. Assessment of the thermal thresholds was labor-intensive and time-consuming and, therefore, analyses of this modality were limited to a random sample of 62 subjects (52 with and 10 without erectile dysfunction).

Erectile function. The status of erectile function was determined by assessing responses on the "erectile function domain" of the IIEF questionnaire.[14,15] The IIEF was scored on a 1 to 30 scale. A score of 25 or greater indicated absence of dysfunction and a score of less than 25 identified patients with erectile dysfunction.[14,15]

Data analysis. Variables were assessed initially with univariate methods to determine the shape of each distribution, and assess any deviations from assumptions necessary for subsequent modeling (Tukey). Penis sensitivity measures (vibration, touch, spacial perception, hot thermal threshold, cold thermal threshold) and locations (base, frenulum, glans) were compared for optimal utility through hierarchical multiple regression analysis (STATA, 2001, Statistical Software, College Station, Texas) whereby stepwise modeling was used to rank the measures and locations, and assess the differential R^2 for each additional measure. Cut scores were then determined for the best measures using logistic regression (SAS, 2002, Statistical Software, Cary, North Carolina) to determine (statistical) sensitivity, and specificity, and to develop and compare receiver operator curves (ROC).

RESULTS

A total of 107 patients were recruited for this study from the population visiting the urology clinic at Montefiore Medical Center in 2001 and 2002. Patient sampling was largely by convenience and willingness to participate in the study but we made every attempt to enter a representative sample of the clinic population. While many subjects are referred to the clinic for erectile dysfunction, others are seen for urological evaluation of nonerectile problems. The demographics of the patients included in the study are presented in table 1. Approximately 36% of the subjects were white, 26% black, 26% Hispanic and 11% unidentified. Of the cohort evaluated 24 subjects (22%) scored within the normal range and constituted the no erectile dysfunction group (control), while 83 subjects (78%) had evidence of erectile dysfunction by history (erectile dysfunction group). Several demographic factors clearly distinguished subjects in the control and erectile dysfunction groups. Subjects with erectile dysfunction were significantly older, less likely to be white and more likely to have diabetes. The sensory measures obtained at each of the locations on the penis are presented in table 2 along with the number of subjects evaluated with each modality and test site.

Mixed models repeated measures analysis of variance (SAS PROC MIXED), controlling for age, diabetes and hypertension, revealed that sensory modality (warm thermal threshold, cold thermal threshold, spatial perception, vibration and pressure) was predictive of IIEF score ($F = 209$, $df = 4,1315$, $p < 0.001$), while the site of measurement was not. To determine the best method of measurement, we used hierarchical regression, which revealed that warm tempera-

TABLE 1. *Sample description*

	Dysfunctional		Controls	
Total No. pts.	83		24	
No. white (%)	24	(29)	15	(63)
No. black (%)	27	(33)	1	(4)
No. Hispanic (%)	24	(29)	4	(17)
No. unknown (%)	8	(10)	4	(17)
No. hypertension (%)	30	(36)	7	(29)
No. diabetes (%)	22	(27)	2	(8)
Mean age (SD)*	53.6	(14.5)	46.1	(14.9)
Mean IIEF score (SD)	13.2	(6.0)	28.6	(1.6)

* Groups differ, $p < 0.05$.

TABLE 2. *Threshold scores for each testing modality and assessment site on the penis*

	Dysfunctional		Controls	
	Mean (No.)	SD	Mean (No.)	SD
Spatial perception (tactile circumferential discriminator):				
Base	6.62 (42)	1.48	5.06 (17)	1.56
Frenulum	6.90 (42)	1.30	5.47 (17)	1.94
Glans	6.38 (73)	1.60	4.83 (23)	1.78
Vibration (biothesiometry):				
Base	7.02 (42)	4.86	4.06 (16)	0.85
Frenulum	7.73 (41)	6.91	4.31 (16)	1.35
Glans	7.84 (73)	6.87	3.82 (22)	1.68
Pressure (Semmes-Weinstein monofilaments):				
Base	10.57 (41)	46.4	0.93 (17)	0.82
Frenulum	11.17 (41)	46.4	1.08 (17)	1.34
Glans	7.43 (70)	35.6	0.83 (23)	1.00
Cold threshold glans	25.0 (52)	2.5	28.3 (10)	2.41
Warm threshold glans	39.5 (52)	2.0	36.0 (10)	1.89

ture was the best predictor of erectile dysfunction with pseudo $R^2 = 0.19$, $p < 0.0007$. Logistic regression was used to determine optimal cut scores for erectile dysfunction using the warm temperature measure. Using 37C and greater yielded a sensitivity of 88.5%, specificity 70.0% and positive predictive value 85.5% (fig. 1).

The ROC curve in figure 1 is a graph representation of test accuracy where larger area under the curve represents better test accuracy. The curve also demonstrates the relationship between sensitivity (patients truly have erectile dysfunction) and specificity (patients truly have normal erectile function) where most decisions tradeoff one for the other. The defining points in figure 1 show that at 0,0 no one has erectile dysfunction and 100% false-negatives are recorded, while at 100,100 everyone has erectile dysfunction and 100% of false-positives are also recorded.

In the absence of thermal threshold measurements, hierarchical regression determined that spatial perception at the glans was the next best measure of erectile dysfunction with pseudo $R^2 = 0.20$, $p < 0.001$. Logistic regression was used to determine optimal cut scores for erectile dysfunction using the spatial perception (tactile circumferential discriminator) measure. Using 5 and greater yielded a sensitivity of 86.3%, specificity 56.5% and positive predictive value 79.2% (fig. 2).

DISCUSSION

The urologist is frequently asked to evaluate patients with complaints of erectile dysfunction. While the treatment algorithm may not be altered (that is sildenafil is first line therapy) with a specific diagnosis, patients and physicians alike believe that it is important to establish the etiology of impotence.[16] Diagnostic testing for this condition commonly involves a complete history and physical examination, often supplemented with questionnaires, vascular testing, neurophysiological testing, pharmacological testing and overall functional assessment, for example nocturnal penile tumescence testing. The ideal test for each category would be easy to perform, noninvasive, low cost to physician and patient, quickly performed, and have a high sensitivity and specificity.

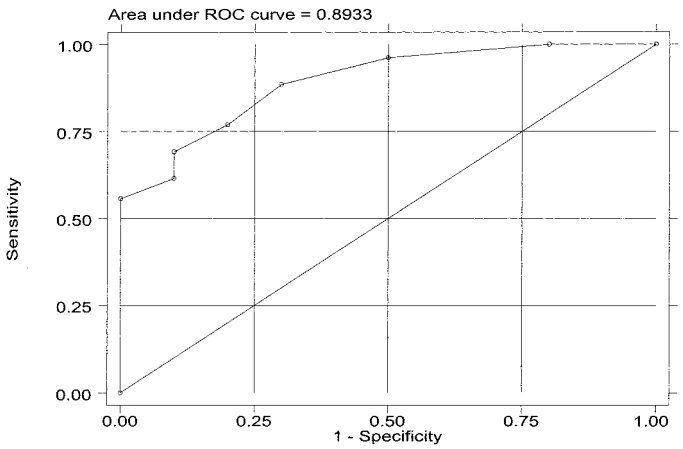

FIG. 1. Receiver operator curve for erectile dysfunction using warm temperature discriminations.

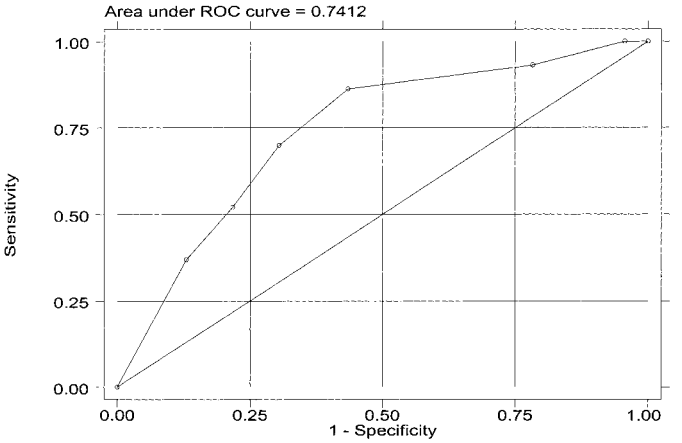

FIG. 2. Receiver operator curve for erectile dysfunction using spatial perception (tactile circumferential discriminator).

Numerous diagnostic tests have been used to assess the neurological function of the penis, including quantitative somatosensory testing, bulbocavernosus reflex, corpus cavernosum electromyogram signal assessment, somatosensory evoked potentials and anal or urethral sphincter electromyography.[2–9] Currently, none of these tests is considered the gold standard for neurological assessment. Despite this fact, quantitative somatosensory testing offers many advantages, including noninvasiveness, ease of performance and use in a longitudinal fashion.[9] Our goal was to determine which quantitative somatosensory test was the best for determining neurological functioning and whether location of testing impacted results.

Location of neurophysiological testing of the penis has not been well described. Biothesiometry, the most widely used quantitative somatosensory test, has been performed on the ventral glans, dorsal glans and penile shaft[17,18] but comparisons among these locations have not been addressed. Penile thermal thresholds have also been performed on the dorsal aspect of the penile shaft, as well as the dorsal aspect of the glans.[8,9] We examined 3 locations on the penis including the dorsal glans, ventral middle penile shaft and dorsal base of the penile shaft. Using biothesiometry, spatial perception and pressure sensation we demonstrated that site of testing was not an important determinant for the diagnosis of erectile dysfunction. Although not significantly better, we preferred to perform testing on the dorsal glans. We found the dorsal glans to be an easily accessible, available, easily standardized and well published location.

Although location of testing does not affect prediction of IIEF score, clearly the method of testing was important. We were able to demonstrate that warm thermal threshold was the best method of predicting the IIEF score and that the addition of another method did not significantly improve results. Warm thermal thresholds evaluate the unmyelinated C fiber pathway. In the penis free nerve endings derived from thin myelinated or unmyelinated C fibers make up 80% to 90% of all axon terminals in the human glans.[19] Our results are consistent with the known anatomy of the penis. In the absence of thermal thresholds we found that spatial perception was the next best method. When the small fiber function testing is removed, large fiber testing remains

a valuable method to assess nerve function with a sensitivity of 86.3% and a specificity of 56.5%.

Quantitative somatosensory testing of the penis evaluates the overall nerve functioning of the penis but is not able to discriminate the contribution of various factors (for example age, diabetes) to the overall result. In a recent study we evaluated the contribution of age, diabetes and hypertension to the results obtained with each of the 5 tested modalities.[9] Hypertension did not significantly contribute to the differences between controls and those with erectile dysfunction. Also age significantly impacted vibration, and diabetes significantly impacted vibration and warm thermal thresholds but that they did not obscure the overall differences between normal subjects and patients with erectile dysfunction. While diabetes (and presumably other well-defined neurological causes) and age have an impact on some of the testing modalities, the clinical importance of testing is evaluating the overall neurological function and not the specific contribution of each aspect of the history of the patient.

CONCLUSIONS

Quantitative somatosensory testing of the neurological status of the penis is a well established diagnostic technique. Currently, validated equipment and procedures exist to test vibration, pressure, spatial perception, warm, cold and painful stimuli. Our goal was to provide well controlled, standardized sensory stimuli to evaluate the condition of the penile nervous system. Although any of these methods may be easily and appropriately used for penile neurological testing, it is not feasible to perform all measurements in a clinical setting. Ideally, neurological status could be assessed with 1 measurement that could be performed rapidly. If a patient needed a 5C difference from acclimation temperature to differentiate warmth then he was considered to have abnormal function. With this 1 recording we were able to demonstrate that a single QST of warm thermal thresholds can be used to assess the neurological status of the penis with good sensitivity and specificity. This test can be performed in less than 5 minutes, and is noninvasive, office based and highly predictive of neurological penile impairment. These QST modalities can be used to assess all patients presenting with complaints of erectile dysfunction to determine the presenting neurological status, neurological response to therapies and disease related progression longitudinally.

The Physitemp NTE-2A Thermal Sensitivity Tester was provided by Physitemp Instruments, Clifton, New Jersey.

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